

Protocol

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This supplementary folder includes the following items:

- TOPARP Protocol Version 1
- TOPARP Protocol Version 2
- TOPARP Protocol Version 3
- TOPARP Protocol Version 4
- Summary of Changes
- Main Statistical Analysis Plan
- Biomarker Statistical Analysis Plan

TOPARP

Phase II Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer

Chief Investigator Prof. Johann de Bono

Co-Sponsors: The Royal Marsden Hospital NHS Foundation Trust /
The Institute of Cancer Research

Approval: Clinical Trials Advisory & Awards Committee
(CTAAC)

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The TOPARP trial has been scientifically approved
by Cancer Research UK's Clinical Trials Advisory & Awards Committee (CTAAC)
The TOPARP trial is part of the National Institute for
Health Research Clinical Research Network Trial Portfolio



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This protocol describes the TOPARP trial and provides information about procedures for entering patients. The protocol should not be used as a guide for the treatment of other patients. Every care has been taken in the preparation of this protocol, however corrections or amendments may be necessary. These will be circulated to investigators in the trial. Centres entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version. Protocol amendments will be circulated to participating centres as they occur.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended. It will be conducted in compliance with the protocol, the Data Protection Act (Z6364106) and other regulatory requirements as appropriate.

Glossary of Abbreviations and Definitions of Terms

AD	Androgen deprivation
ADP	Adenosine diphosphate
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase (SGPT)
APTT	Activated partial thromboplastin time
AST	Aspartate Transaminase (SGOT)
AR	Androgen receptor
AZ	AstraZeneca
BID	Twice daily
BER	Base excision repair
BP	Blood Pressure
BUN	Blood urea nitrogen
°C	Degrees Celsius
FBC	Full Blood Count
cm	Centimetre
CR	Complete Response
CrCl	Creatinine clearance
CRF	Case Report Form
CRPC	Castration Resistant Prostate Cancer
CT	Computerised Tomography
CTC	Circulating Tumour Cell
CTCAE	Common Terminology Criteria for Adverse Events
D	Day (as in treatment day)
dL	Decilitres
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DRE	Digital rectal exam
DSB	Double Strand Breaks
DW-MRI	Diffusion-weighted MRI
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
FDA	Food and Drug Administration
FISH	Fluorescent in-situ hybridisation
FBC	Full Blood Count
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyltransferase
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
Ha	Alternative Hypothesis
H2AX	Histone H2AX
Ho	Null hypothesis
HR	Homologous Recombination
IB	Investigator Brochure
IC50	Dose for 50% inhibition
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IF	Immunofluorescence
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRB	Institutional Review Board
ITT	Intention To Treat
kg	Kilogram
LD	Longest Diameter
LDH	Lactic Dehydrogenase
LHRH	Luteinizing Hormone Releasing Hormone
mg	Milligram
MRI	Magnetic Resonance Imaging
miRNAs	MicroRNAs
NAD	Nicotine adenine dinucleotide
NCI	National Cancer Institute
NCICTC	National Cancer Institute Common Terminology Criteria
nM	Nanomolar
NRS	Numeric Rating Scale
ORR	Overall Response Rate
PARP	Poly (ADP-ribose) polymerase
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD	Pharmacodynamic
PFS	Progression Free Survival
PICF	Patient Informed Consent Form
PIN	Prostatic Intraepithelial Neoplasm
PK	Pharmacokinetic
PO	Per Oral (by mouth)
PR	Partial Response
PSA	Prostatic Specific Antigen
PCWG2	Prostate Cancer Working Group 2
PT	Preferred Term
PTEN	Phosphatase and Tensin Homologue
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SD	Stable disease
SUSAR	Serious unexpected suspected adverse (drug) reaction
SBP	Systolic blood pressure
SSB	Single Strand Break
SOC	System Organ Class
μM	Micromolar
ULN	Upper Limit of Normal
UA	Urinalysis
WBC	White Blood Cells

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1 TRIAL SUMMARY

PROTOCOL TITLE	Phase II Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer (TOPARP).
TARGET DISEASE	Castration resistant prostate cancer (CRPC)
STUDY OBJECTIVES	<ul style="list-style-type: none"> To evaluate the anti-tumour activity of olaparib in metastatic castration resistant prostate cancer To identify molecular signatures of tumour cells in responding and non-responding patients To clinically qualify putative predictive biomarkers of PARP inhibitor sensitivity
STUDY DESIGN	Open-label, single arm, two part adaptive design phase II trial.
TRIAL POPULATION	Patients with an advanced CRPC who have failed androgen deprivation and taxane-based treatment.
TREATMENT REGIMEN	Patients will receive single agent olaparib 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.
RECRUITMENT TARGET	Part A: between 30-45 patients Part B: 44 patients
PRIMARY ENDPOINT	Response will be defined on the basis of the following outcomes, if any of these occur patients will be considered to have responded: <ul style="list-style-type: none"> Objective response by modified RECIST PSA decline of $\geq 50\%$ according to the Prostate Cancer Working Group 2 (PCWG2) Conversion of circulating tumour cell count (CTC) from ≥ 5 cells/7.5 ml blood at baseline to < 5 cells/7.5 ml confirmed by at least two readings 4 weeks apart
SECONDARY ENDPOINTS	<ul style="list-style-type: none"> Radiological progression free survival Time to radiological progression Progression free survival Overall survival Time to PSA progression Proportion of patients with conversion of CTC count from $\geq 5/7.5$ml blood at baseline to $< 5/7.5$ ml blood nadir Duration of PSA response and objective response (PSA-ORR), if applicable Safety and tolerability of olaparib
EXPLORATORY ENDPOINTS	<ul style="list-style-type: none"> To evaluate the impact of treatment with olaparib on bone metastasis imaging by DW-MRI in selected patients and to correlate these results with PSA, CTC and radiological responses

	<p>by conventional imaging.</p> <ul style="list-style-type: none"> To determine the proportion of patients achieving pain improvement with olaparib treatment.
<p>TRIAL OUTLINE</p>	<ul style="list-style-type: none"> There will be screening period of up to 28 days prior to cycle 1 day 1. Archival tissue is mandated for enrolment into the study. Patients who do not have a prior histological diagnosis or archival tissue available will be required to have a tumour biopsy. PART A of the study will be open to all comers. In PART B the tumour tissue of the patients being considered for enrolment will be analysed first to ensure the presence of the putative predictive biomarkers and only patients with the predictive biomarkers will be enrolled. Patients will receive single agent 400mg of olaparib, twice daily, continuously on 28-day cycles. During the study period, no other anticancer or hormonal treatment will be given although a LHRH analogue must be continued, unless the patient is surgically castrate. <p>Efficacy Assessments:</p> <ul style="list-style-type: none"> Baseline CT scans, bone scan and DW-MRI (optional) will be performed as close as possible to cycle 1 day 1 of treatment. These scans will be repeated after every 3 cycles (12 weeks) or earlier if clinically indicated. PSA will be assessed at baseline and every 12 weeks by PCWG2 criteria. In the absence of radiological disease progression patients should continue on study. <p>Safety Assessments:</p> <p>Safety parameters will be continuously assessed throughout the study prior to each cycle of treatment. Adverse events (AEs) and serious adverse events (SAEs) including laboratory tests will be graded and summarised according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events version 4.02 (CTCAE v4.02).</p> <p>Based on Phase I and Phase II studies, olaparib is generally well tolerated. Safety concerns are mainly related to the possibility of myelosuppression. Patients who experience a NCI-CTCAE grade 3-4 haematological or non-haematological toxicity that the investigator attributes to olaparib may have an interruption of olaparib treatment for up to 42 days until recovery of all toxicities to no more than NCI-CTCAE grade 1. Those patients on continuous treatment requiring a delay in dosing by >14 days will require a dose reduction to 300mg BID. If the adverse event recurs at the same severity, treatment can be interrupted again and on resolution to ≤ NCI-CTCAE grade 1 toxicity a further dose reduction to 200 mg BID can be made. If the adverse event recurs despite the second dose reduction a final dose</p>

	<p>reduction to 100mg BD is permitted.</p> <p>Olaparib should be withheld in the event of:</p> <ul style="list-style-type: none"> • Grade 4 neutropenia • Grade 2-4 neutropenia with infection • Platelet count lower than $50 \times 10^9/L$ • Non-haematological toxicity grade 3 or greater, except nausea, vomiting or diarrhoea and fatigue associated with suboptimal pre-medication and/or management OR transient and clinically insignificant biochemical blood results. • Aspartate transaminase (AST) or alanine transaminase (ALT) elevations grade 3 or higher for more than 7 days. • Any other toxicity that, in the view of the principal investigator and the medical monitor, represents a clinically significant hazard to the patient until resolution of toxicity to no more than grade 1. <p>Biomarker Assessments:</p> <p>All patients enrolled in the study are required to have archival tumour tissue, fresh tumour biopsies, blood and urine samples collected during the study for the purpose of biomarker analyses including the following:</p> <ul style="list-style-type: none"> • Circulating tumour cells (CTCs): enumeration & molecular characterisation • PTEN and ERG immunohistochemistry (IHC) on primary tumour tissue and fresh paired biopsies • PTEN and ERG immunofluorescence (IF) in CTCs • <i>TMPRSS2-ERG</i> and <i>PTEN</i> fluorescence in situ hybridisation (FISH) studies in primary tumour, paired biopsies and CTCs • γH2AX and RAD51 foci formation in paired tumour biopsies and CTCs • Markers of tumour cell proliferation and cell cycle phase in paired tumour biopsies and CTCs • Circulating plasma tumour DNA • Circulating plasma tumour and whole blood RNA • Urine telopeptides and RNA • Proteomic profile • Metabonomic profile
FOLLOW UP	<p>Patients will be treated until disease progression (radiological progression) or withdrawal from the study for another reason. After discontinuing study treatment patients will be reviewed 30 +/- 5 days post cessation of treatment for an end of study safety assessment.</p>

2 INTRODUCTION

2.1 Metastatic Castration Resistant Prostate Cancer

Prostate cancer is the second leading cause of male cancer-related mortality in the United Kingdom (1). While a proportion of patients have indolent disease, curable with local treatment, approximately a third of patients fail local treatment and develop incurable metastatic disease. Androgen deprivation therapy constitutes the mainstay of treatment for advanced prostate cancer. Most patients with advanced disease initially respond to hormonal deprivation therapy; however resistance inevitably develops within 1-3 years and represents a transition to more aggressive and invariably fatal disease. Recent studies have established that androgen signalling continues to play a pivotal role in tumour progression as castration resistance evolves. Androgen receptor (AR) gene amplification, AR overexpression, AR activating mutations and the presence of sufficient intratumoural androgen levels contribute to continued AR signalling despite a systemic castrate state. The recent emergence of the CYP17 inhibitor, abiraterone and other novel antiandrogens such as MDV3100 provide clinical validation that targeting AR signalling remains a useful approach in a significant proportion of CRPC patients (2, 3).

Metastatic prostate cancer is often associated with significant disease-related morbidity. The vast majority of these patients develop bone metastasis with clinical sequelae of bone pain, skeletal fractures, spinal cord compression and haematological compromise. In addition, soft tissue disease is liable to cause urinary obstructions and other problems.

Most CRPC patients have received multiple lines of hormonal manipulation prior to commencing chemotherapy for ongoing disease progression. Docetaxel and more recently cabazitaxel, Sipuleucel-T, alpharadin and abiraterone have demonstrated an overall survival advantage for metastatic CRPC (mCRPC) albeit of only several months (2, 4, 5, 6). Despite these important incremental advances in treatment options, benefits remain modest and the median survival of patients with mCRPC is unsatisfactory at approximately 18 – 36 months. It is clear that there is an urgent need for better treatments that offer durable clinical benefit and further improvement in overall survival for these patients.

Platinum Based Second-line Chemotherapy in Patients with CRPC

Platinum-based chemotherapy in Phase II trials has provided encouraging response rates (PSA and radiological) in the range of 44-60% and a median progression free survival (PFS) of 4-9.5 months in the post-docetaxel CRPC setting (7, 8). Likewise, satraplatin, an orally bioavailable platinum compound, has shown second-line antitumour activity in unselected patients in a Phase III trial, with a 50% PSA decline rate of 33% and a statistically significant PFS advantage in 40% of the patients (9). The lack of survival outcome in this study, despite the anti-tumour activity observed, may in part relate to inter-patient molecular heterogeneity and failure to optimally select the subgroup of tumours most likely to respond to this strategy.

Platinum salts induce interstrand and intrastrand DNA cross-links and consequently increased levels of double-strand (ds) DNA damage. Platinum compounds and PARP inhibitors (PARPi) exert their anti-tumour activity in a similar way by inducing increased ds-DNA breaks which overwhelms the DNA repair machinery in homologous recombination (HR) repair deficient tumours, consequently resulting in tumour cell death. Tumour sensitivity to the Poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib has been shown to correlate with prior platinum sensitivity in HR deficient, *BRCA1/2* mutant cancers (10, 11). It follows therefore that the previously established antitumour activity for satraplatin in prostate cancer supports the widely held premise that there is indeed a subgroup of CRPC that harbour HR DNA repair defects and will benefit from treatment with the PARP inhibitor, olaparib. No platinum is currently approved for the treatment of CRPC; indeed most CRPC remain platinum naïve. Recruitment of patients most likely to benefit based on biomarker driven molecular sub-classification is critically important for the successful development of novel therapies such as olaparib in this disease.

Prostate Cancer Heterogeneity: Clinical and Molecular

Prostate cancer is a highly heterogeneous disease with patients responding differently to treatments and overall having very different clinical outcomes. This is also reflected at a molecular level (12-16). Different molecular variants portend different clinical outcomes possibly secondary to distinct differences in molecular drivers. Despite this, to date, Phase III trials of novel anticancer drugs in this disease have failed to stratify patients on the basis of molecular profile and likely benefit. This inter-patient molecular heterogeneity may, in part, account for the high risk of failure of pivotal Phase III trials of anticancer drugs in this disease. We envision that an improved understanding of the biological and clinical significance of the molecular sub-classification of this disease will positively impact pivotal randomised clinical trials in this disease. The identification of primary tumour prognostic and predictive molecular markers as compared to the currently utilised suboptimal clinicopathological parameters will allow improved patient selection for optimal CRPC treatments thus maximising clinical benefit while avoiding unnecessarily exposure and toxicity in patients unlikely to benefit.

Dissecting Prostate Cancer Heterogeneity by FISH: *PTEN* & *ETS* Gene Rearrangements.

Functional Loss of *PTEN*

Prostate cancer can be molecularly sub-classified using multi-colour fluorescent in situ hybridisation (FISH). Dissecting the molecular profile of prostate cancers in this way has resulted in the characterisation of multiple commonly occurring genetic aberrations implicated in promoting tumour genesis (12, 15, 17, 18). The biological significance of gene rearrangements, deletions and amplifications as well as possible predictive and prognostic relevance are currently being extensively studied. Phosphatase and tensin homologue (*PTEN*), a tumour suppressor gene, negatively modulates the phosphatidylinositol 3-kinase (PI3)/AKT signal transduction pathway which fosters tumour growth, proliferation and survival (19-22). Bi-allelic and mono-allelic deletion of *PTEN* is a common event in prostate cancer and is implicated in tumour pathogenesis and progression (22-25). *PTEN* functional loss is associated with more advanced disease, higher-grade tumours and a worse clinical

outcome (15, 24-27). The frequency of reported *PTEN* inactivation in prostate cancer is variable in the literature, with mono-allelic and bi-allelic loss by FISH in the range of 30-68% (23, 26, 27, 28). Our own analysis has shown a complete loss of *PTEN* expression by immunohistochemistry (IHC) in archival tissue in approximately 50% in patients on the abiraterone phase I-II studies. The variability seen in the literature may be related to tumour stage, tissue processing, and IHC methodology. A recent study of tumour material from 59 patients with CRPC revealed that the *PTEN* gene was deleted in 77% of cases; 25% with homozygous deletions, 18% with homozygous and hemizygous deletions and 34% with hemizygous deletions. Bi-allelic *PTEN* loss was correlated with disease-specific mortality in this study (24).

Evidence for the importance of *PTEN* functional loss in prostate carcinogenesis also comes from transgenic studies. Critically, conditional *PTEN* loss in prostates from transgenic mice leads to the late development of metastatic prostate cancer (29). Prostate restricted overexpression and activation of *AKT*, however, resulted only in prostatic intraepithelial neoplasia (PIN) formation (30). These data suggest that *PTEN* loss may possibly induce prostate carcinogenesis not only through its phosphatase PI3K/*AKT* regulatory role but also possibly through its nuclear, DNA repair, role that has been recently reported (31, 32).

***TMPRSS2* Chromosomal Translocation**

Chromosomal translocation involving the androgen-responsive gene transmembrane protease serine 2 (*TMPRSS2*) with the oncogenic erythroblast transformation specific (*ETS*) transcription factor family of genes (*ETV1*, *ETV4*, *ETV5*) is reported in 50%-70% of prostate cancers (17, 33). *TMPRSS2/ERG* is the predominant type of gene fusion seen and results in overexpression of 3'-*ERG* sequence joined to the 5'-*TMPRSS2* promoter. Less frequently *TMPRSS2* becomes fused to *ETV1* and *ETV4*. *ERG* and other *ETS* family members are transcription factors that are implicated in the control of cell growth and differentiation. *TMPRSS2/ERG* fusion rearrangement has been shown to co-operate with *PTEN* haploinsufficiency to promote carcinogenesis (17, 22, 34) and accounts for continued hormone driven disease (35). Recent evidence implicates topoisomerase IIB-mediated DNA breakage during the induction of transcriptional programs in generating these *TMPRSS2/ERG* fusion rearrangements (36, 37, 38).

We have utilised validated FISH assays to evaluate *PTEN* deletions and the commonest *ETS* gene rearrangements (*ERG* and *ETV1*) on the Trans-Atlantic Prostate Group (TAPG) tissue microarray (TMA) (15). We demonstrated that patients with *PTEN* loss (heterozygous or homozygous: 17% of newly diagnosed cancers) had significantly worse cause-specific and overall survival compared with patients with no *PTEN* loss, supporting the haploinsufficiency proposed for the *PTEN* gene (Figure 1). Three hundred and eight patients with both *ETS* gene (*ERG* and *ETV-1*) rearrangement and *PTEN* loss status available were analysed for survival outcome (Figure 2). The largest group of patients (n=167, 54%) had no *ERG* or *ETV-1*-gene rearrangement and no *PTEN* loss and had the best outcome with 85.5% survival at 11 years. A poor prognosis group was also identified (n=19, 6%) who had *PTEN* loss but no *ERG* or *ETV-1*-gene rearrangement with a cause-specific survival of 13.7% at 11 years and a median survival of 5 years from diagnosis. Patients with an *ETS* gene rearrangement with or without *PTEN* loss had an intermediate prognosis in keeping with the hormonal sensitivity of these cancers, which has recently

been described (15, 27). Overall, therefore, these data indicate that prostate cancer is a molecularly heterogeneous disease, with cancers demonstrating PTEN loss having a poor outcome, and that to accelerate the successful development of targeted therapies in CRPC, identifying the appropriate subgroup of patients most likely to benefit is paramount.

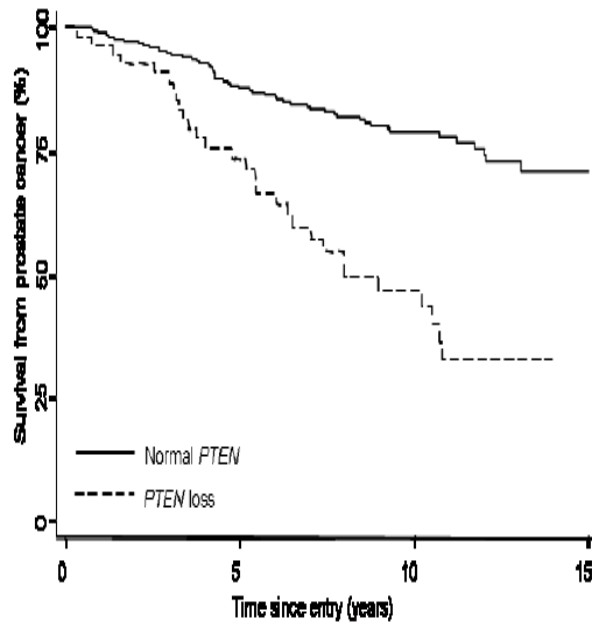


Figure 1: PTEN loss prostate cancers have a worse overall survival

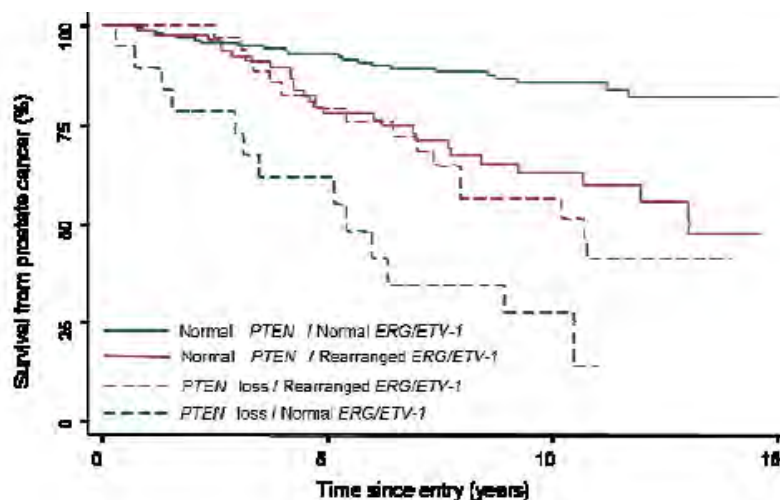


Figure 2: Multi-colour FISH based stratification by studying *ETS* rearrangements and PTEN loss.

PTEN Loss, *ETS* Gene Rearrangements and HR Repair Defects

PTEN is implicated in many functions, both PI3K/AKT dependent and independent. Recent reports suggest in addition to lipid phosphatase function, PTEN localises to the nucleus and that its function includes maintenance of genomic stability (31, 32) by a number of mechanisms including interacting with CENP-C an integral centromeric binding and

stabilising protein, regulating the transcription of RAD51, a critical DNA double strand break (DSB) repair protein (39) and modulating cell cycle progression (40).

PTEN loss results in impaired HR DNA repair with reduced RAD51 expression, increased chromosomal aberrations and genomic instability (31,39). Moreover, in vitro cell-based experiments and in vivo xenograft studies have established that PTEN deficient tumour cells much like *BRCA1/2* deficient tumours are selectively sensitive to platinum compounds and potent PARP inhibitors including olaparib (41-43). Furthermore, restoration of PTEN expression in PTEN deficient tumour cell lines restores PARP inhibitor resistance, confirming PTEN as a determinant of the response to PARP inhibition. This synthetic lethal relationship between PTEN-null tumours and PARP inhibition supports the therapeutic utility of PARP inhibitors in PTEN-deficient tumours. Moreover, *ERG*, the oncogene driven by the commonest prostate cancer genetic driver lesion *TMPRSS2/ERG*, has been shown to directly associate with PARP and requires PARP for its transcriptional regulatory function with PARP inhibition having antitumour activity in *ERG* rearranged tumour models (44,45).

Given these pre-clinical observations and the putative role of PTEN in maintaining chromosomal stability, we predict that tumours with PTEN loss and /or *ETS* gene rearrangements are likely to be hypersensitive to PARP inhibition. We therefore aim to evaluate the antitumour activity of olaparib in patients with sporadic CRPC using an adaptive biomarker driven design to identify and clinically qualify predictive biomarkers of olaparib sensitivity for optimal patient selection.

2.2 PARP and PARP Inhibition

Poly(ADP-ribose) polymerase 1 (PARP-1) is a zinc-finger DNA-binding enzyme that is activated >500 fold upon binding to DNA double or single strand breaks (46). PARP-1 (113 kDa) and PARP-2 (62 kDa) are thus far the only members of the PARP enzyme family known to be involved in DNA damage signalling and repair with a degree of functional redundancy between these proteins. PARP-1 signals the presence of DNA damage and plays a critical regulatory role in DNA damage repair. PARP-1 is involved in a wide range of cellular processes including DNA repair and maintenance of genomic integrity, regulation of protein expression at the transcriptional level, regulation of cellular replication and differentiation, regulation of telomerase activity, and involvement in the cell apoptotic pathway (47).

PARP-1 comprises 3 domains, the N-terminal DNA-binding domain containing 2 zinc fingers, the auto-modification domain and the C-terminal catalytic domain. PARP-1 binds to both single and double-stranded DNA breaks through the zinc-finger domain and catalyses the cleavage of nicotinamide adenine dinucleotide (NAD)⁺ into nicotinamide and ADP-ribose, and subsequently transfers successive units of ADP-ribose onto DNA, histones, PARP-1 and other DNA repair proteins to form branched ADP-ribose polymers. These branched ADP-ribose polymers result in post-translational modification of histones and other nuclear proteins which convert the DNA damage signal into intracellular signals that activate either DNA base-excision-repair (BER) pathways or cell death if the damage is beyond repair. Other transcriptional factors and signalling molecules are also poly-ADP-

ribosylated by PARP-1 to initiate a multitude of other important cellular functions (47,48). Given the critical role that PARP plays in single strand DNA repair it is not surprising that PARPi are able to potentiate the cytotoxic damage incurred with DNA-damaging chemotherapy agents and ionizing radiation (49). PARP inhibitors have also shown significant single agent activity in tumours with HR deficiency (10,11, 50,51).

Synthetic Lethality Between *BRCA1/2*-mediated Homologous Recombination Repair and PARP-1

Abrogating PARP dependent BER, which is responsible for repairing DNA single strand breaks (SSBs) results in the accumulation of SSBs. These SSBs collapse at the replication forks during DNA synthesis giving rise to double strand breaks (DSBs) that are detrimental to the cell. The DNA DSBs are preferentially repaired by high fidelity HR repair that restore genomic integrity under normal circumstances. *BRCA1* and *BRCA2* genes encode proteins that are essential in HR repair. *BRCA1/2* deficient tumour cells lack HR repair capacity and are therefore unable to repair these replication associated DSB DNA damage, which accumulates in the context of suppressed PARP activity, leading to chromosomal instability, cell cycle arrest and apoptosis. The profound selective sensitivity of *BRCA* deficient tumour cells for PARPi compared with unaffected heterozygous mutant normal tissue retaining one functional *BRCA* allele provides a large therapeutic window (47,52,53).

Preclinical models have demonstrated that HR deficient tumour cells with *BRCA1*^{-/-} and *BRCA2*^{-/-} genotype are exquisitely sensitive to PARP inhibition with olaparib (previously referred to as KU-0059436 or AZD2281 in earlier studies), in contrast to heterozygous mutant or wild-type cells (52). Likewise, in the clinic, olaparib is an efficacious therapy with durable antitumour activity and a favourable toxicity profile in HR deficient tumours arising in *BRCA1* and *BRCA2* mutation carriers including several patients with mCRPC (11).

Epigenetic Disruption of *BRCA 1/2* Function and Other Causes of HR Impairment

It has been hypothesised that targeting SSB DNA repair with PARPi will be a useful therapeutic strategy in sporadic tumours that harbour HR repair defects. This may occur due to either epigenetic or genetic silencing of *BRCA1/2* function or disruption of any of the other key proteins that make up the HR repair pathway. Loss of *BRCA 1/2* function may arise spontaneously via somatic mutations and epigenetic mechanisms during tumour formation. These somatic mechanisms of *BRCA1/2* functional loss are increasingly implicated in sporadic carcinogenesis (54,55). Epigenetic gene silencing of tumour-suppressor genes is a well-recognised phenomenon with methylation of the *BRCA1* promoter found in 11-14% of sporadic breast cancers and 5-31% of ovarian cancers (56). Epigenetic modification of the Fanconi anaemia/*BRCA* pathway through promoter hypermethylation in lung, oral cancer and cervical cancer cell lines render these cells highly sensitive to DNA cross-linking agents (57,58). Somatic mutations of *BRCA* genes and heterozygous loss also appear to be more common than previously defined (54,58,59). The term “BRCAness” is commonly used to describe the phenotypic likeness of a sporadic tumour with a familial-*BRCA1/2* mutation related cancer (56). Identification of this BRCAness phenotype secondary to epigenetic / genetic silencing of the Fanconi anaemia/*BRCA* pathway may select for clinical benefit from PARPi in these sporadic cancers.

In addition to somatic *BRCA1/2* dysfunction, disruption of any of the other critical proteins that make up the HR repair pathway such as RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHEK1, CHEK2, FANCD2, FANCA or FANCC 2 have been shown in preclinical models to cause HR deficiency and render these tumour cells highly susceptible to synthetic lethality with PARPi (56, 60, 61).

Clinical evidence supporting single agent olaparib antitumour activity in sporadic cancer was recently reported (58,62,63), with durable objective responses observed in 28% of sporadic high grade serous ovarian cancers in one study and a further study reporting a significant improvement in progression free survival (62,63). These responses may be explained in part by the high frequency of somatic mutations of *BRCA1/2* as well as epigenetic silencing of this and other key HR genes in high grade serous ovarian cancer (58). These results have led to the further evaluation of single agent olaparib in other tumour types enriched for HR defects. Identifying the subgroup of sporadic tumours with HR defects through validated predictive biomarker studies is imperative, if we are to successfully develop novel treatments such as PARP inhibitors (PARPi) and personalise medicine.

There has been limited investigation to date of the incidence of somatic aberrations in key HR related genes in advanced prostate cancer. High penetrance germline mutations in several candidate genes involved in DSB repair including *BRCA1*, *BRCA2*, *CHEK2*, *BRIPI/FANCI* and *NBS1* are known to account for a small fraction of prostate cancer cases (64-70). *PTEN* however is one of the commonest tumours suppressor genes that is deregulated in prostate cancer and is implicated in the pathogenesis of this tumour as discussed above. Loss of *PTEN* function may also result in deficient HR DNA repair with reduced RAD51 expression and sensitivity to PARP inhibition (39,41). Likewise, the *ERG/TMPRSS2* gene rearrangement which is observed in 50% of prostate cancers is also implicated in conferring sensitivity to PARPi (44). Overall, these data support the evaluation of PARP inhibitors in the treatment of advanced prostate cancer.

2.3 Rationale for Study

Despite recent advances in CRPC treatment, metastatic prostate cancer remains a common disease with a poor outlook. Improved treatments that offer durable clinical benefit and significant survival impact remain an area of unmet medical need. As with most chemotherapies, a proportion of prostate cancers will not respond due to the underlying tumour biology and inherent resistance mechanisms. Understanding the underlying molecular determinants of response and resistance to different treatments is critical for improvement in CRPC patient outcome through optimally selected treatments.

The previously established antitumour activity of platinum based regimens in advanced prostate cancer suggests that there is a subgroup of CRPC susceptible to DNA damaging agents such as platinum and PARPi.

The PARP inhibitor, olaparib is a novel anticancer agent with strong preclinical and clinical data for significant antitumour activity in HR repair deficient tumours arising in *BRCA1* and

BRCA2 mutation carriers including a number of patients with metastatic CRPC (10,11,50,51,52,53). Recent clinical evidence supports the utility of this approach in sporadic high-grade ovarian cancers enriched for HR defects (62,63). Moreover, there is a growing body of preclinical evidence that supports extending this approach to a wide range of other sporadic tumours with disruption to other non-redundant components of the HR repair pathway including RAD51 and other essential HR repair proteins (60,61). Identifying these sporadic tumours with HR repair defects through validated predictive biomarkers remains a challenge and focus of ongoing research.

PTEN loss has been implicated to confer HR DNA repair defects with reduced RAD51 expression, increased genomic instability and tumour sensitisation to PARP inhibition (41-43). Homozygous *PTEN* loss by FISH is present in 20-30% of CRPC, with loss of protein expression by IHC being far more common (21). In addition, the *TMPRSS2/ERG* driver rearrangement, which is present in approximately 50-60% of prostate cancers and co-associates with *PTEN* loss has also been reported to confer sensitivity to PARP inhibition (44,45).

The target population for this trial are patients with advanced metastatic CRPC progressing following docetaxel treatment. A proportion of patients may also have received treatment with abiraterone and cabazitaxel. Given the high prevalence of loss of *PTEN* function and *TMPRSS2/ERG* rearrangements in this population and the strong preclinical rationale for this therapeutic strategy, we anticipate that a subgroup of these patients will benefit from olaparib treatment.

Patients may continue olaparib treatment until disease progression or treatment intolerance. Patients may however withdraw from the study at any point if they choose to do so or if the investigator believes it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for reducing the dose of olaparib are provided.

Rationale for Circulating Tumour Cell Based Studies in CRPC

Enumeration of circulating tumour cells (CTC) number using the Cell Search system (Veridex, PA) is a valid biomarker to monitor the effectiveness of therapy of patients with metastatic breast cancer (71-73), colorectal cancer (74) and prostate cancer (75-78). High baseline counts have consistently been associated with more aggressive disease and a worse outcome (76-78). CTC counts are highly prognostic for overall survival, and CTC count falls post-treatment associate with an improved overall survival and response to therapy in CRPC. In a pilot study, univariate analysis demonstrated that CTC counts of < 5/7.5 ml blood or ≥ 5 /7.5 ml blood correlated with OS (0.002; HR=7.37); in multivariate analyses CTC counts and PSA doubling time were the only 2 independent predictors of outcome unlike PSA, Gleason score, presence and absence of bony metastasis and age (75). In a similar study that related changes in CTC counts in patients with CRPC during the first 2 cycles of treatment with clinical outcome, we observed that patients with CTC counts that remained below 5 cells/7.5 ml blood during treatment with cytotoxic therapy had the best outcomes, whilst patients whose counts changed from ≥ 5 /7.5 ml blood to ≤ 5 had improved outcomes compared to the patient cohort whose CTC count remained persistently

elevated at $\geq 5/7.5$ ml blood throughout treatment. In addition, patients whose CTC counts increased during treatment from < 5 to $\geq 5/7.5$ ml blood had a similar poor outcome to the group whose count remained persistently elevated at ≥ 5 CTCs throughout treatment suggesting the development of treatment resistance (76). CTC counts were commonly detected in patients with advanced CRPC; CTC counts $>5/7.5$ ml were detected in 19/49 (39%) and 21/28 (75%) of chemotherapy –naïve and post–docetaxel patients respectively treated on the phase I-II Abiraterone studies (35). We now have data from almost a thousand patients participating in the randomised Phase III abiraterone trial (COU-301) that CTC conversion from ≥ 5 to <5 as well as any fall in CTC from 10% to 90% count post-treatment at 1, 2, 3 months after starting abiraterone is a statistically robust surrogate/intermediate endpoint of overall survival, meeting all of Prentice's criteria for surrogacy (78)

In addition, CTCs have been shown to retain many of the genomic characteristics of the primary tumour and thus provide a useful opportunity to study molecular changes in the disease profile longitudinally with ongoing treatment. Multicoloured FISH assays have been successfully applied to determine commonly found genomic alterations such as AR amplification, *PTEN* deletions and *TMPRSS2/ERG* fusion rearrangements in prostate CTCs (35,79,80). We have also developed multiplex immunofluorescence assays to evaluate protein expression in CTCs.

Rationale for Radiographic PFS and 6 months PFS as an Endpoint

Clinical research in prostate cancer has been hindered by the difficulty in objectively defining cancer progression. Composite endpoints that include patient reported, radiographic, and skeletal-related events have suffered from subjectivity. Conventional RECIST alone has limitations in CRPC in defining radiographic progression due to the fact that fewer than 50% of men with CRPC have measurable lesions greater than 2cm in size, and most of these lesions are in lymph nodes which impact survival less than visceral metastases (81). Conventional RECIST also lacks the sensitivity to differentiate true progression of bone metastasis from the flare phenomenon on bone scan or CT scan due to healing of previous bone metastasis (82,83). Although radiographic PFS is not a surrogate for overall survival in patients receiving docetaxel therapy, it outperforms PSA based progression (83).

Attribution of disease progression due to tumour flare phenomenon will be mitigated in this study by applying the new consensus guidelines that requires a confirmatory bone scan at least six weeks after the original scan to define progression. This will reduce the number of false positive determinations of CRPC progression. (Refer to Appendix D)

Progression of metastatic bone disease is of paramount importance to CRPC patients since it is responsible for severe morbidity of skeletal related events such as fracture, pain, and spinal cord compression. Similarly, progression of soft tissue metastasis may be associated with clinically significant morbidity. Prevention or delay in cancer progression should result in clear clinical benefit to the patient. In conclusion, radiologic PFS (rPFS) is an objective measurement that may associate with clinical benefit in the proposed study population.

Pain and Analgesic Assessments

Pain due to bone metastases and nerve root compression is a common experience for patients with advanced prostate cancer. Pain has previously been shown to significantly associate with overall survival in advanced prostate cancer. The McGill Pain Questionnaire (MPQ) (PPI score 0-2 versus 3-5) successfully stratified the survival of first line chemotherapy patients in TAX 327 (84,85).

The BPI-SF, a numeric rating scale (NRS), has been selected as the pain instrument for this study due to the high correlation of numeric rating scales with verbal descriptor scales (e.g. MPQ PPI) (86) and its prior use in other metastatic prostate cancer studies (87,88). The BPI-SF assesses both the intensity of pain and the interference in the patient's function caused by their pain (89). The BPI-SF data can potentially help illustrate the overall benefit of treatment on pain. Analgesic usage will be scored according to the WHO analgesic ladder: 0 for no analgesic, 1 for non-opioid analgesics (including NSAIDs, paracetamol/acetaminophen, antidepressants, and agents intended to treat neuropathic pain), 2 for opioids for moderate pain, and 3 for opioids for severe pain (90).

3 BACKGROUND THERAPEUTIC INFORMATION

Olaparib

Olaparib previously referred to as AZD2281 or KU-0059436 in earlier studies is a potent inhibitor of PARP-1. Olaparib shows significant monotherapy activity in tumour cells with defective components of HR, such as cells with the *BRCA1* *-/-* and *BRCA2* *-/-* genotype both preclinically and clinically (10,11,50,51,52,53,62,63). Selective tumour sensitivity to this PARP inhibitor has also been observed in tumour cells with loss of PTEN function and *ETS* gene rearrangements (41,42,44). This sensitivity in pre-clinical models is expected to translate to clinical benefit.

3.1 Pre-clinical Experience with Olaparib

This pre-clinical and clinical experience with olaparib (AZ2281, KU0059436) is fully described in the Investigator Brochure (IB). Key findings are summarised below.

Pharmacokinetic Data

The olaparib molecule shows cellular activity in the low nM range with a cellular dose for 50% inhibition (IC₅₀) of 2 nM in HeLa cells. Distribution of olaparib is typical for an orally administered foreign compound, in the gastro-intestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. The oral bioavailability of olaparib when dosed at 5mg/kg via a solution formulation was 17% and 19% in male and female rats and 79% *-/+* 12 in male dogs. An oral study of olaparib demonstrated bioavailability of >85% for both 5% and 20% w/w microionised dispersion of the drug substance in Gelucire. Following single oral dosing (5mg/kg), absorption was rapid with an AUC of 10.3 \pm 2.01 in

dogs. The estimated $t_{1/2}$ for olaparib was 3.0, 2.5 and 4.61 \pm 1.66 hours in female rats, male rats and dogs respectively. Multiple oral dosing of olaparib in 28-day rat and dog studies demonstrated that absorption was rapid and exposure increased greater than proportionally with dose across the dose range examined (upto 15mg/kg/ day in dogs and upto 40mg/kg in rats). Plasma protein binding of olaparib varied between 70.4% and 58.8% in rat and dog studies. Metabolism data to date is limited and further investigations are ongoing. To date, several metabolites have been observed in pre-clinical studies. Similar metabolite profiles were observed in the urine and faeces of male and female rats. Excretion is primarily via the faeces and to a lesser extent, the urine. In a study of [14 C]-olaparib in the rat, excretion was 76 \pm 13% in faeces and 20 \pm 11% in urine. For more detailed preclinical data please refer to the IB.

Toxicology and Safety Data

Olaparib has shown comparatively low toxicity in rodent and dog toxicology studies. Oral doses of olaparib were well tolerated for up to 6 months in safety studies and showed no cardiovascular, respiratory, central, peripheral and autonomic nervous system toxicity findings that were a concern. The toxicology studies indicate that the target organ of toxicity is the bone marrow. Specific *ex vivo* work has been conducted exposing human bone marrow cells to olaparib, which has confirmed that olaparib is also active against human bone marrow. The cytotoxic effect becomes evident at a higher concentration than that which fully ablates PARP activity (mean IC₅₀ of 2.7 μ M for myelosuppression [n = 4 human donors] compared with 0.1 μ M for total PARP-1 activity inhibition). These data, along with the 28-day dog and rat studies, show a myelotoxic effect that is mild-to-moderate and is reversible. Platelets appear first affected, followed by white blood cells. Importantly, oncology clinics are used to monitoring for the onset of such effects and are expert in their management.

Olaparib showed no mutagenic potential in the Ames test. Olaparib was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test, and was genotoxic in the rat micronucleus test. Reproductive toxicology data indicate that olaparib can have adverse effects on embryofetal survival and development at dose levels that do not induce maternal toxicity. These findings are not uncommon for many therapeutic agents used in oncology, and so do not present an unacceptable risk when appropriately clinically managed. For further details on these tests or on the fertility studies please refer to the IB.

3.2 Clinical Experience with Olaparib

3.2.1 Pharmacokinetic (PK), Pharmacodynamic (PD) Data

In the Phase I study, patients with solid tumours were given olaparib at a starting dose of 10mg for the first 14 days of a 21-day cycle with a subsequent protocol amendment, changing the dose schedule to continuous daily dosing starting at 100 mg BID for a 28-day cycle. Absorption was rapid and a peak plasma concentration was observed between 1-3 hours post dosing with a terminal elimination half-life of 6.10 hours, supporting twice daily dosing. Drug exposure increased dose proportionally with doses up to 100 mg but increase less than dose proportionally thereafter. The mean volume of distribution and mean plasma

clearance are approximately 40.3 L and 4.55 L/h. On multiple dosing, there was no evidence of any time dependency of the PK and no marked accumulation. Exposure increased proportionally with dose at doses up to 100 mg twice daily but increased in a less than proportional fashion at higher doses. There was no evidence of any marked ethnic difference in PK of olaparib between Japanese and Caucasian patients. Following dosing to cancer patients at doses of 400 mg BID, the population estimated maximum plasma concentration at steady state ($C_{max\ ss}$) ranged from 1.45 $\mu\text{g}/\text{mL}$ to 11.0 $\mu\text{g}/\text{mL}$ (3.34 μM to 25.3 μM , equivalent to unbound concentrations of 0.26 $\mu\text{g}/\text{mL}$ to 1.99 $\mu\text{g}/\text{mL}$ [0.6 μM to 4.58 μM]); the steady state area under the plasma concentration-time curve (AUC) (area under plasma concentration-time curve from zero to 12 h [AUC₀₋₁₂]) ranged from 6.56 $\mu\text{g}\cdot\text{h}/\text{mL}$ to 122 $\mu\text{g}\cdot\text{h}/\text{mL}$.

The distribution of olaparib is typical for an orally administered compound, in the gastrointestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Following administration of a radiolabelled dose of olaparib to cancer patients, olaparib accounted for approximately 70% of the circulating material in the plasma with the remainder accounted for by 3 other components (each accounting for approximately 10% of the material), all of which were also present in the excreta. Drug-related material was eliminated in the urine (35% to 50%) and in the faeces (12% to 60%) with 10% to 20% and 0.6% to 14% of the dosed material recovered in the urine and faeces as unchanged drug, respectively. A further 35 and 19 drug related components were excreted in the urine and faeces, respectively. The metabolites produced were predominantly a consequence of hydroxylation, oxidation or dehydrogenation of the piperazine carboxycyclopropyl, the flourophenyl and the phthalazinone ring system.

Evidence of inhibition of PARP-1 activity has been seen in peripheral blood mononuclear cells (PBMC) and tumour samples from patients dosed with olaparib at all dose levels studied (10 mg to 600 mg) but the data shows wide inter-individual variability in the extent of inhibition achieved and no evidence of any relationship between extent of inhibition and dose administered. Concentration-response curves for inhibition of PARP-1 activity in both PBMC and tumour samples have been generated from a population PK-PD analysis of the data. The population average maximal extent of inhibition in PBMC and tumour samples were 50.6% and 70%, respectively, with maximal inhibition achieved at plasma exposures (steady state AUC) in excess of 1 $\mu\text{g}\cdot\text{h}/\text{mL}$ (exposures which would be expected to be reliably achieved following doses of >40 mg). The potential clinical benefit of continuous dosing is supported by preclinical studies, which show that tumours re-grow after short-term use (e.g. 14 days) and that continuous PARP inhibition with olaparib was able to prevent tumour re-growth. The maximum tolerated dose of olaparib established in the Phase I trials was 400 mg twice daily, continuously (10).

3.2.2 Efficacy Data

The phase I study was enriched with *BRCA1* and *BRCA2* mutation carriers with advanced tumours in the escalation and expansion phase given the strong preclinical rationale of selective tumour killing in *BRCA1/2*-deficient cell lines. In the Phase I study, 41% of 46 evaluable patients with *BRCA*-mutant ovarian cancers achieved objective responses

(complete or partial responses) either by Gynecologic Cancer Intergroup (GCIG) CA125 or RECIST criteria and a further 11% of patients attained RECIST disease stabilisation (10,11). The encouraging clinical benefit rate of >50% in the subpopulation of *BRCA1/2* mutation cancer patients provides compelling evidence of single agent PARP inhibitor activity in *BRCA*-deficient cancer patients. Durable antitumour responses have also been reported in *BRCA* mutated breast and prostate cancer patients with one prostate patient ongoing treatment for more than 2 years (10, 11, 50, 51).

Two parallel open-labelled multicentre phase II studies of olaparib in *BRCA1/2* mutation carriers with advanced breast and ovarian cancer have confirmed the significant therapeutic efficacy of PARPi in this population (50, 51). 54 breast cancer patients and 56 ovarian cancer patients with advanced heavily pre-treated disease were recruited to 2 non-randomised sequential dose cohorts of 400mg and 100mg BID of olaparib. Following efficacy assessment of the 2 dose levels; patients on the 100mg BID cohort in both studies were allowed to increase the dose of olaparib to 400mg BID given the improved antitumour activity seen at the higher dose level. The breast cancer study reported an objective response rate (ORR) of 41 % (11/27) with 1 complete response (CR) and 10 partial response (PR)s and a median progression free survival (PFS) of 5.7 months (m) (range 4.6-7.4m) at 400mg BID in contrast to an ORR of 22% (6/27) with 6 PRs and a median PFS of 3.8m (range 1.9-5.5m) at the lower dose level (27). In the ovarian study, patients on the 400mg BID and 100mg BID dose levels showed an ORR of 33% (11/33) versus 13% (3/24) by RECIST criteria, a response by either RECIST or by GCIG criteria of 61% (20/33) versus 17% (4/24) and a median duration of response of 290 days (range: 126-513 days) versus 269 days (range:169-288 days) respectively (50). Both dose levels demonstrated clinical activity, however the 400mg BID was more efficacious with improved outcomes establishing substantial antitumour activity for olaparib at a dose of 400mg BID in heavily pre-treated, *BRCA* mutant advanced breast and ovarian cancer patients (50,51). A further phase II study of olaparib at 400mg BID in patients with sporadic high grade ovarian cancer showed an objective response rate of 28%. This study provided the first clinical evidence for the antitumour activity of olaparib in sporadic serous ovarian cancers (62). Most recently, patients with sporadic platinum sensitive serous ovarian cancer who previously achieved either a partial or complete response from platinum therapy demonstrated a doubling of the progression free survival (PFS) from 4.8months to 8.4months with 400mg BID olaparib maintenance treatment compared to placebo. The hazard ratio (HR) was 0.35 (95% CI: 0.25, 0.49; p<0.00001) (63).

3.3 Summary of Clinical Toxicity Data

The clinical experience with olaparib is fully described in the IB and largely has been conducted with the Gelucire® 44/14 (capsule) formulation.

As of 20 May 2011, 1645 patients suffering from ovarian, breast and a variety of other advanced solid tumours had been exposed to olaparib across the dose range 10 mg daily to 600 mg BID, either as monotherapy (n=12 studies) or in combination with other chemotherapy agents (liposomal doxorubicin, cisplatin, dacarbazine, gemcitabine,

gemcitabine+cisplatin, carboplatin, carboplatin+paclitaxel, paclitaxel, topotecan, irinotecan, or bevacizumab).

Data from these studies indicate that olaparib is generally well tolerated at doses up to 400 mg BID as monotherapy in patients with solid tumours. Administration of olaparib has been associated with laboratory findings and/or clinical diagnoses of:

- Haematological toxicity:
 - Anaemia, generally mild to moderate (CTCAE grade 1 or 2)
 - Neutropenia, predominantly mild to moderate (CTCAE grade 1 or 2)
 - Thrombocytopenia, generally mild to moderate (CTCAE grade 1 or 2), sometimes severe (CTCAE grade 3 or 4)
 - Mean corpuscular volume or elevation, generally mild to moderate (CTCAE grade 1 or 2)
- Nausea and vomiting, generally mild to moderate (CTCAE grade 1 or 2), intermittent and manageable on continued treatment
- Dyspepsia, generally mild to moderate (CTCAE grade 1 or 2)
- Dysguesia, generally mild to moderate (CTCAE grade 1 or 2)
- Fatigue, generally intermittent of mild to moderate intensity (CTCAE grade 1 or 2)
- Headache, generally mild to moderate (CTCAE grade 1 or 2)
- Dizziness, generally mild to moderate (CTCAE grade 1 or 2)
- Pneumonitis events with no consistent clinical pattern have been reported rarely in a small number of patients
- Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML) have been reported very rarely in a small number of patients

From the completed studies, there are no safety concerns noted for the renal or hepatic parameters measured and no clinically significant changes of concern relating to coagulation parameters. The changes in haematological parameters (haemoglobin, neutrophils, and thrombocytes) are as expected for olaparib monotherapy or can be explained by co-existing conditions/previous chemotherapy.

Olaparib appears to be generally well tolerated at PARP inhibitory dose levels in the monotherapy clinical studies with predominantly mild toxicity. Thus it represents a potential

advance in the treatment of advanced cancers by directly inhibiting PARP-1 and hence tumour growth as monotherapy.

Preliminary data from Phase I and Phase II studies of olaparib in combination with various chemotherapy agents indicate a substantial increase in neutropenia, thrombocytopenia and anaemia compared to giving these cytotoxic agents alone. These findings are consistent with pre-clinical findings. There are more severe haematological events i.e., CTCAE grade 4 neutropenia, febrile neutropenia and thrombocytopenia being reported as SAEs. When these toxicities occur it has been managed with routine clinical practise, including dose delays, dose reductions and intermittent doses and/or the use of supportive care measures such as G-CSF.

Final laboratory data from D0810C00002 (KU36-92) study have shown mean corpuscular volume (MCV) increases in approximately 30% of patients in the study, especially with prolonged treatment with olaparib (≥ 6 cycles of treatment). The MCV elevations were mild to moderate in intensity, observed in the 200 mg BID dose cohort and above and were asymptomatic in nature. There was no obvious correlation of MCV with haemoglobin, platelets or white blood cell (WBC) values for these patients, and there does not appear to be any clinical consequences. MCV has not been captured as a standard laboratory parameter within the olaparib Phase II studies D0810C00008 (KU36-44) and D0810C00009 (KU36-58), however elevations in MCV were also observed in a number of patients from these studies. The MCV elevations again appear to become progressively elevated over time. Elevations in serum amylase were observed in approximately 15% of patients from final laboratory study data from D0810C00002 (KU36-92). The majority of these increases (13%) were mild to moderate (CTCAE grade 1 or 2) with no apparent link to clinical symptoms. No new significant safety information has emerged from any other reported studies with respect to elevations in serum amylase.

Rare Adverse Events

Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML)

As of May 2011 there have been 5 reports of MDS and 4 reports of AML in a total of 6 patients (0.36%) from 5 monotherapy studies out of a total of 1645 patients. Additionally, there has been a further report in one patient out of 294 patients that received olaparib or the comparator (0.34%), in this case pegylated liposomal doxorubicin. The 6 patients received between 6 months and 32 months of olaparib treatment prior to the diagnosis of MDS/AML. In all 6 cases there were other contributory factors that may offer an alternative explanation for the development MDS/AML. All but one patient were also known to be a *BRCA1/2* mutations carrier, another factor that may predispose them to developing MDS/AML. Five of the 6 patients with MDS/AML had other cancers that preceded the diagnosis of ovarian/peritoneal cancers. The ovarian/peritoneal cancer was diagnosed between 2 to 12 years before these patients were commenced on olaparib treatment. These patients were heavily pre-treated with multiple agents including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents over a long duration of time (2 to 17 years) prior to starting olaparib treatment. One patient had a family history of leukemia. Four of the 6 patients have died one from MDS, two from AML and one from disease progression. For 2 of these patients, the MDS/AML syndrome was diagnosed post

completion of olaparib treatment. Epidemiological studies indicate that the incidence of AML/MDS is in the range of 7-8% in ovarian cancer patients who received prior alkylating agents at the 5 year mark (91) and 0.4% at the 2 year mark in first line ovarian cancer patients (92). The cumulative risk of AML/MDS observed with olaparib treatment is in line with the rate quoted at the 2 year mark for first line ovarian cancer patients.

Pneumonitis

As of May 2011 there have been 7 (0.42%) reported cases of pneumonitis or suspected pneumonitis from a total of 1645 patients. Three were from monotherapy studies and 4 were from combination studies (3 from olaparib + liposomal doxorubicin and 1 from olaparib + topotecan). These patients had a variety of cancer types including breast cancer, nonsmall cell lung cancer, small cell lung cancer and cancer of the thymus. All but one of these patients were hospitalised for the management of pneumonitis. Five of these patients have died; 2 from pulmonary insufficiency and 3 for disease progression. In summary, the 7 reported cases of pneumonitis presented with no consistent clinical pattern and were heavily confounded by a number of predisposing factors (including disease under investigation, underlying pulmonary disease, pre-existing medical conditions, smoking history and/or previous chemotherapy and radiotherapy). The frequency of pneumonitis seen with olaparib treatment is consistent with the expected rates of pneumonitis in a cancer population (93-94).

Pre-clinical and Clinical Experience with New Melt-Extrusion (tablet) formulation

Melt-Extrusion (tablet) formulation has been developed to render the olaparib amorphous and presents the drug in a solid dispersion in copovidone (30% drug loading). The milled extrudate is then blended with pharmacopoeial excipients and compressed into a tablet.

The Melt-Extrusion (tablet) formulation, when dosed to fasted dogs at a 100 mg dose, shows at least 2.4 times the C_{max} & AUC than the Gelucire® 44/14 (capsule) formulation. In addition the Melt-Extrusion (tablet) formulation showed reduced pharmacokinetic variability in the dog with CV of ~ 20% as compared to ~ 50% for the Gelucire® 44/14 (capsule) formulation. It is envisioned that the new Melt-Extrusion formulation of olaparib should provide a more bioavailable and patient friendly formulation by minimising the number of dosage units and providing a more consistent PK profile.

This olaparib Melt-Extrusion formulation (tablet) will be the formulation evaluated in the Phase III clinical programme and consequently this study will also be conducted with the olaparib tablet. There is an ongoing trial (D0810C00024) being conducted at the Royal Marsden NHS Foundation Trust and other centres to establish the comparative bioavailability of the tablet formulation compared with the capsule formulation. In addition single and multiple dose safety & tolerability data will be gathered.

Following single oral dosing with the tablet formulation, absorption was more rapid than the capsule. The C_{max} was typically achieved between 0.5 hours and 2 hours after dosing. Following the peak, plasma concentrations declined biphasically with the mean terminal t_{1/2} of 6.97 hours. The mean volume of distribution of olaparib tablet was 54.9L and the mean

plasma clearance was 542L/h. Both G_{mean} , C_{max} and AUC increased approximately proportionally with dose (8-fold and 12-fold, respectively, for a 10-fold increase in dose).

The relative bioavailability (BA) of the tablet formulation (compared to capsule) at the 3 lower dose levels studied are shown in Table 1. At the 2 lower tablet doses, although the C_{max} achieved after dosing with the tablet formulation tended to be higher than that with the capsule, when based on AUC, the BA of the 2 formulations was actually very similar. However, at the highest tablet dose (250 mg), the exposure delivered by the tablet formulation (both C_{max} and AUC) was higher than that delivered by the capsule.

Table 1: Relative bioavailability of tablet versus capsule formulation

Parameter	25mg tablet dose vs 50mg capsule dose	50mg tablet dose vs 100mg capsule dose	250mg tablet dose vs 400mg capsule dose
C_{max} ratio	1.29	1.53	2.49
95% CI	0.92-1.81	1.17-2.00	1.93-3.20
AUC ratio	1.03	0.99	1.74
95% CI	0.83-1.27	0.71-1.38	1.27-2.38

AUC, Area under the plasma concentration-time curve; CI, Confidence interval; C_{max} , Concentration maximum(plasma).

On multiple dosing, a 200mg tablet BID dose gave plasma exposure within the range of those achieved following 400mg BID capsule dose (6.88ug/ml vs 5.71 ug/ml) but the average AUC_{0-12} and C_{min} were lower (36.1ug/ml vs 43.1 ug/mL and 1.00ug/mL vs 1.86ug/mL, respectively) than achieved in a separate cohort of patients following the 400mg BID capsule dose. In addition, steady state data generated from a further cohort of patients randomised to BID dosing with both 200mg tablets and 400mg capsule dose (n=6) demonstrated that the 2 formulations could not be concluded to be bioequivalent (treatment ratio for C_{max} was 0.99 (90% CI:0.85 to 1.15) but for AUC_{0-12} was 0.79 (90% CI:0.65 to 0.94). Following multiple doses at 250, 300, 350 and 400mg BID, exposure continued to increase with dose. Please refer to the IB for further data on the tablet formulation.

The dose escalation phase of the ongoing Phase I bioavailability trial (D0810C00024) has been completed and has shown 400 mg BID to be the maximum tolerated tablet dose with frequent dose limiting toxicities being observed at higher doses. The study is now further evaluating the tolerability and clinical activity of two tablet doses - 300 mg BID and 400 mg BID. Preliminary data suggest that 400mg BID olaparib tablets is well tolerated over the first 4 weeks of treatment. In this trial the starting dose of olaparib tablets will be 400mg BID. It is envisioned that a proportion of patients will require dose reductions to 300mg BID, 200mg BID or 100mg BID respectively for cumulative toxicity over the course of several months of treatment.

4 TRIAL OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to evaluate the anti-tumour activity of olaparib in patients with advanced CRPC who have progressed following one or two chemotherapy regimens including taxane-based regimens.

4.2 Secondary Objectives

The secondary objectives are to evaluate:

- Radiological progression-free survival (rPFS)
- Time to radiological progression
- Progression free survival (PFS)
- Overall survival
- Time to PSA progression
- Duration of PSA response (decline of $\geq 50\%$)
- PSA objective response (PSA-ORR)
- The utility of CTCs as an early indication of benefit from PARPi therapy
- Further characterise the safety profile of olaparib in advanced CRPC patients

4.3 Tertiary/exploratory Objectives

- To evaluate clinical benefit as indicated by an improvement in pain measurements (BRI-SW)
- To evaluate DW-MRI imaging in selected patients and to correlate these results with PSA, CTC and radiological responses by conventional imaging

5 TRIAL ENDPOINTS

5.1 Primary Endpoints

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

- Objective response by modified RECIST (baseline lymph node size must be ≥ 2 cm to be considered a target lesion) (Appendix E) or
- Conversion of circulating tumour cell count (CTC) from $\geq 5/7.5$ ml blood at baseline to $< 5/7.5$ ml blood nadir confirmed by at least two readings 4 weeks apart or
- PSA decline of $\geq 50\%$ (according to the PCWG2) (Appendix D)

Failure will be defined as;

- Progression by RECIST – increase in measurable lesion size (S) or new lesion AND/OR
- Progression by bone scan – see Appendix D

5.2 Secondary Endpoints

- Radiological progression-free survival (rPFS)
- Time to radiological progression
- Progression free survival (PFS)
- Overall survival
- Time to PSA progression
- Duration of PSA response (decline of $\geq 50\%$)
- PSA objective response (PSA-ORR)
- Proportion of patients with conversion of CTC count to $< 5/7.5\text{ml}$ blood nadir
- Safety and tolerability profile of olaparib in patients with metastatic CRPC

5.3 Tertiary/exploratory Endpoints

- Impact of olaparib treatment on bone metastases imaged by DW-MRI in selected patients (optional) and to correlate these results with PSA, CTC and radiological responses by conventional imaging
- Proportion of patients achieving pain improvement

6 TRIAL DESIGN

This study is divided into 2 parts; Part A & B. Part A is an efficacy screening stage for sensitive biomarkers. It is designed as an open-labelled, non-randomised two stage design both to allow the activity of olaparib in unselected advanced CRPC patients to be evaluated and to permit the development of predictive biomarkers of response to olaparib. Part B is a subsequent validation stage which will be undertaken if confirmation of activity in a biomarker defined subgroup is necessary. It is an open-labelled, single stage assessment of anti-tumour activity of olaparib in preselected patients based on putative biomarkers of HR repair deficiency previously identified in Part A. A total of up to 89 evaluable patients will be enrolled to Parts A & B.

Patients with advanced CRPC who have consented to participate in this trial will be screened and enrolled into either Part A or Part B of the study depending on which part of the study is running at the time of patient enrolment. Patients will be administered oral olaparib tablets, 400mg BID continuously until disease progression is documented and confirmed (i.e., confirmed radiographic progression) or withdrawal for another reason (see section 10.10). Paraffin embedded tumour blocks or sections from the archival tumour tissue at the time of the original diagnosis or from a biopsy / resection of metastatic disease is mandated from all subjects who enrol on the study. These samples should be obtained during the screening period after written informed consent has been obtained. All patients participating in this trial (Part A & B) will also have mandatory circulating tumour cells (CTCs), plasma and fresh tumour biopsies collected at pre-specified times during the study (Table 2). The tumour material will be analysed for biomarkers of sensitivity (response) to PARP inhibition. These tests will include *PTEN* and *ERG* expression, *ETS* gene

rearrangements and *PTEN* deletions, markers of cell cycle, DNA damage and repair including geminin expression, RAD51 and gamma H2AX foci formation, etc. Other biomarkers identified to be relevant to HR pathway from other translational research may be studied in parallel. Response to treatment with olaparib will be correlated to all the biomarkers evaluated.

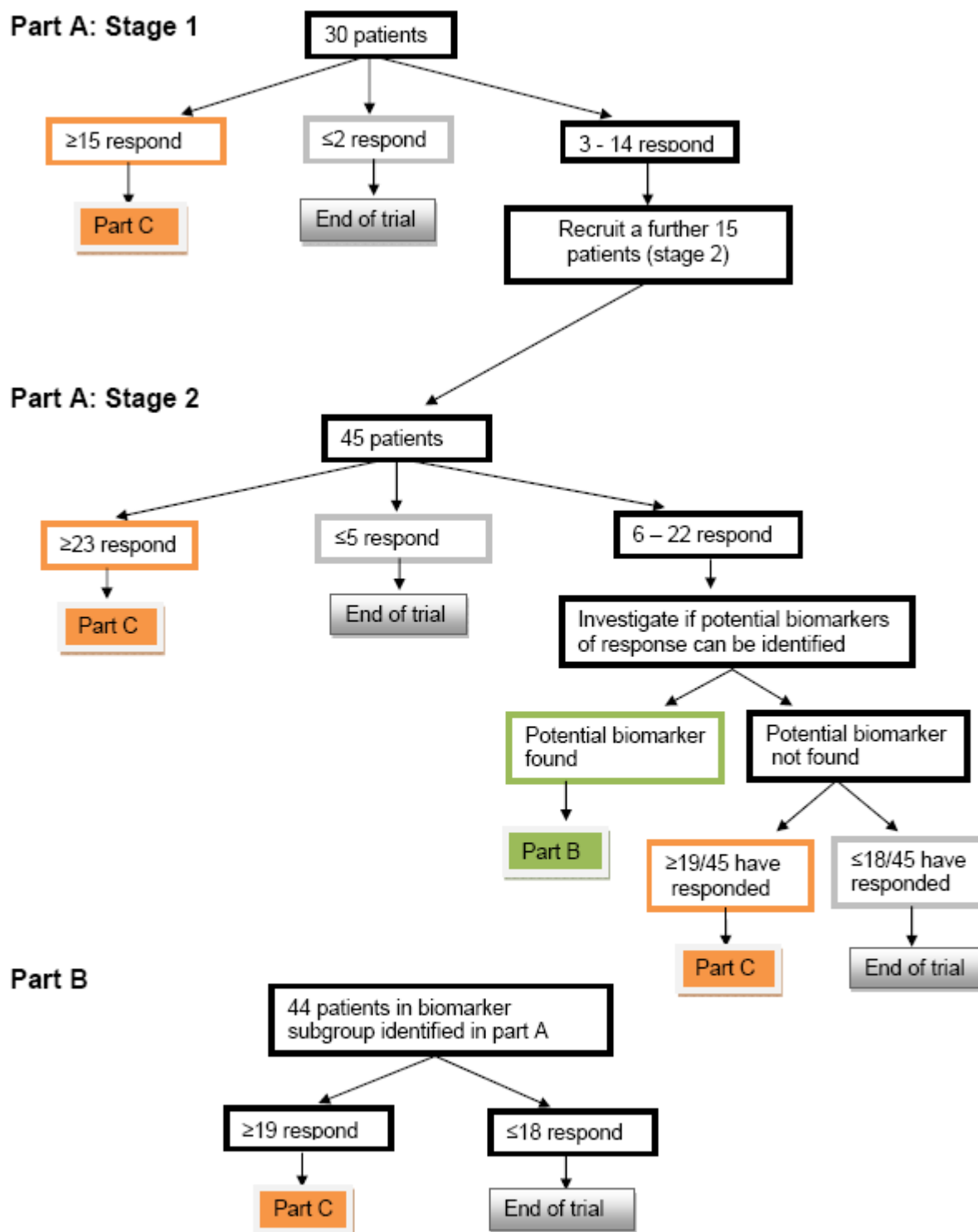
In PART A, accrual will be in unselected patients. The tumour tissue in responders versus non-responders from Part A will be evaluated to develop a molecular classifier for response to olaparib in CRPC patients that can then be utilised to select patients in Part B in the absence of evidence of a high overall response rate in PART A. Patients registered for Part B will be made aware that their tumour tissue will first be analysed for the relevant predefined biomarkers to determine their suitability for participation following consent in Part B of the study.

Disease status will be assessed at regular intervals during the course of the trial by CTC enumeration, computed tomography (CT) scan and / or on magnetic resonance imaging (MRI), diffusion-weighted MRI (DW-MRI), radionuclide bone scans and PSA. Each site should ideally designate the same reader who will evaluate the images for any one patient for the duration of the trial. Throughout the study, safety and tolerability will be assessed by the recording of adverse events; the monitoring of vital signs and physical examinations; and safety laboratory evaluations. Local laboratories will be used for the safety bloods. An independent Data Monitoring Committee (IDMC) will monitor safety data on an ongoing basis. Patient may continue on olaparib for as long as the patient is free of intolerable toxicity and is, in the opinion of the investigator, deriving clinical benefit. Patients may however elect to withdraw from the study at any point without prejudice to further treatment. Patients will have a safety follow-up visit 30 days +/-5 after their last dose of study drug for safety and end of study assessments.

Although outlined in the trial schema below, Part C is not currently included in this protocol but may be incorporated following completion of Parts A & B as an amendment to this protocol. PART C will be the subsequent randomised evaluation of olaparib versus an appropriate standard of care comparator to be decided at the time of initiating the amendment. Part C will only be initiated if there is sufficient evidence of antitumour activity observed either in the unselected or selected CRPC patients to warrant further evaluation of olaparib in a randomised setting. This will occur following the evaluation of safety, efficacy and biomarker analysis from Parts A and B by the Independent data Monitoring Committee (IDMC) and will involve a separate funding application and regulatory approvals. Patients in Part C may be either preselected patients based on the molecular determinants of response as identified in Parts A and B, or be unselected, depending on the response that has been seen in Parts A and B.

More details on the design of the trial can be found in the statistical considerations section.

6.1 Study Flow Chart



Part C will only be initiated if the anti-tumour activity observed in Parts A and B are sufficient to warrant a randomised study. The design of Part C will be determined following the analysis of Parts A/B.

Figure 3: Adaptive TOPARP Trial Schema

7 PATIENT SELECTION & ELIGIBILITY

Subjects with advanced progressing CRPC (not known to have a germline *BRCA1/2* mutation) who have had either one or two previous lines of taxane-based chemotherapy will be invited to participate in the TOPARP study.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to safeguard the integrity of the study results.

7.1 Number of Patients

Part A: 30-45

Part B: 44

7.2 Source of Patients

Several oncology centres in the United Kingdom with extensive experience in conducting phase II/III trials have agreed to participate in this trial. Patients who have progressing castration-resistant metastatic prostate cancer will be offered participation in this trial.

7.3 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in the study:

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 taxane-based 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:
 - At least 28 days since the completion of prior flutamide treatment. Patients whose PSA did not decline in response to antiandrogens given as a second line or later intervention will only require a 14 days washout prior to Cycle 1, Day 1.
 - 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.

- 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:
 - 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 $\mu\text{g/L}$ (2 ng/ml); patients on systemic glucocorticoids for control of symptoms must have documented PSA progression by PCWG22 while on systemic glucocorticoids prior to commencing Cycle1 Day1 of treatment.
 - 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 $\geq 50\%$)
 9. Life expectancy > 12 weeks.
 10. Patient must be able to swallow a whole tablet.
 11. Patient and the patient's partner of childbearing potential, must agree to use medically accepted methods of contraception (e.g., 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 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:
 - Haemoglobin ≥ 10 g/dL independent of transfusions
 - White blood cells $> 3 \times 10^9/\text{L}$
 - Absolute neutrophil count $\geq 1.5 \times 10^9/\text{L}$
 - Platelets $\geq 100 \times 10^9/\text{L}$
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) except for patients with known Gilbert's syndrome.
 - Aspartate transaminase (AST) (SGOT) and alanine transaminase (ALT) (SGPT) ≤ 2.5 x ULN or ≤ 5 x ULN in the presence of liver metastases.
 - Serum creatinine ≤ 1.5 x 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:

$$\text{GFR} = \text{CrCl (ml/min)} = (140 - \text{age}) \times \text{wt (kg)} / (\text{serum creatinine} \times 72)$$
 - Albumin > 30 g/dl

7.4 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

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 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 have experienced a seizure or seizures within 6 months of study treatment or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in patients not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital (see Section 12.13)).
11. Patients receiving any of the following classes of inhibitors of CYP3A4 (see Section 12.13 for guidelines and wash out periods);
 - 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 investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's 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

7.5 Restrictions

1. Patients must refrain from fathering a child or donating sperm during the study and for 3 months following the last dose of olaparib. Patients of child bearing potential and their partners, who are sexually active must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after the last dose of study drug. Reliable methods of contraception should be used consistently and correctly. Acceptable methods of contraception to be used in this study include:
 - Condom with spermicide and one of the following:
 - Oral contraceptive or hormonal therapy (e.g. hormone implants)
 - Placement of an intra-uterine device
 - Acceptable non-hormonal birth control methods include:
 - Total sexual abstinence. Abstinence must be for the total duration of the study and for 3 months following the last dose of olaparib
 - Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
 - Tubal occlusion plus male condom with spermicide
 - Intrauterine Device (IUD) plus male condom and spermicide - Provided coils are copper-banded
 - Acceptable hormonal methods:
 - Etonogestrel implants (eg, Implanon, Norplan) and male condom with spermicide
 - Normal and low dose combined oral pills+male condom with spermicide
 - Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
 - Intravaginal device and male condom with spermicide (eg, EE and etonogestrel)
 - Cerazette (desogestrel) and male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.
2. No other chemotherapy or other novel agent is to be permitted during the course of the study with the exception of continued used of LHRH agonist. Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be adequately be managed with analgesics as long as the patient does not meet the criteria of disease progression or treatment discontinuation.
3. Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.
4. In vitro data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, **to ensure**

patient safety all patients must avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity (see Section 12.13) from the time they enter the screening period until 30 days after the last dose of study medication.

8 OVERVIEW OF STUDY PROCEDURES

8.1 Informed Consent

The study objectives, overall requirements, potential benefits and risk will be discussed with potentially eligible patients. Interested patients will be given a TOPARP patient information sheet. Consent must be obtained only after allowing the patient sufficient time for consideration, and the opportunity to ask any further questions. A signed, TOPARP written informed consent form must be obtained from the patient in accordance with local practice and regulations. Pre-entry tests, not performed routinely as part of standard patient management, will only be done after the TOPARP consent form has been signed and personally dated by both the patient and the Investigator. Confirmation of the patient's informed consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed form will be provided to the patient and the original retained in the investigator site file and must be available for verification by ICR-CTSU study staff or for regulatory audit/inspection at any time. Patients who consent on the TOPARP study, consent to having fresh tumour biopsies, archival tumour tissue, CTCs and plasma collected for molecular and biomarker studies.

Patients who wish to have diffusion weighted MRI (DW-MRI) scans to assess their disease during the study will be required to sign a specific DW-MRI consent form. Participation in this component of the study is entirely voluntary. Refusal to participate in the DW-MRI component of the study will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.

8.2 Registration

Once informed consent has been obtained, patients must be registered for screening by contacting the ICR CTSU:

To register a patient telephone ICR-CTSU
On: 0208 643 7150
(09.00 – 17.00 Monday to Friday)

The following information will be required when registering the patient:

- Name of cancer centre, treating hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent
- Patients initials and date of birth
- Confirmation of diagnosis

The patient will be allocated a unique registration number.

8.3 Eligibility status and trial entry

Once all screening evaluations have been completed, an eligibility checklist should be completed by the clinician/research nurse. The eligibility checklist should be completed for all patients registered.

For those patients who remain eligible, the clinician / research nurse should contact ICR-CTSU to confirm eligibility and obtain a trial number.

To confirm patient eligibility telephone ICR-CTSU

On: 0208 643 7150

(09.00 – 17.00 Monday to Friday)

The following information will be required:

- Patient's full name, hospital number, NHS number, postcode and trial registration number.
- Confirmation of the patient's eligibility status according to the eligibility checklist
- Confirmation that the evaluable disease being followed in the trial has been assessed by either CT or MRI and a bone scan within 4 weeks of scheduled start date of treatment
- Confirmation of consent for the trial

If the patient is confirmed as eligible for trial entry, the caller will be given the patient's unique trial identification number (Trial ID), and fax confirmation will be sent to the appropriate pharmacist to enable dispensing of the study drug.

A screening log should be completed for all registered patients who do not subsequently enter the study. This will record reasons for exclusion e.g. because screening tests identified that they were ineligible or the patient subsequently withdrew consent.

9 OVERALL STUDY ACTIVITIES

9.1 Screening Period

All patients must sign the TOPARP written informed consent before study specific screening procedures can be performed. Consent may be obtained up to 28 days prior to Cycle 1, Day 1. Patients will have a screening period of up to 28 days prior to Cycle 1 Day 1. The laboratory investigations (haematology, electrolytes, tumour markers, CTCs and testosterone level) must be performed within 14 days of starting treatment on olaparib. For details of the schedule and nature of the screening assessments, refer to Table 2 (page 56). All the screening assessments must be complete and eligibility criteria met prior to enrolment into the study. Patients who meet the eligibility and screening requirements will

return to the site for Cycle 1 Day1 visit. As part of the screening process, CTCs, a pre dose biopsy and blood samples will be collected for the predefined biomarkers of interest.

9.2 Treatment Period

All screening assessments must be completed and reviewed prior to the commencement of Cycle 1 Day 1 assessments. In the event that Screening and Cycle 1 Day 1 visits coincide, Cycle 1 Day 1 assessments do not need to be repeated. Olaparib at a dose of 400mg will be administered orally twice daily, once in the morning and once in the evening, continuously. Patients may receive continuous treatment for as long as they remain free from intolerable toxicity, and, in the investigator's opinion, are receiving clinical benefit. The patient will return on Day 8 and Day 15 of Cycle 1 and subsequently on the first day of each treatment cycle in order to evaluate safety, tolerability and dosing compliance. From Cycle 2 to end of study patients' Day 1 visits will occur on a 28 day cycle with a +/- 2 day window. If the study window is utilised every effort will be made for the patient to return to schedule. Patients will have additional imaging visits up to 8 days before Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1, after every 3 cycles thereafter and end of study. For details of the schedule and nature of the ongoing assessments, refer to Table 2. The dose of olaparib may be reduced and/or a treatment delayed in patients experiencing toxicities according to the dose modification guidelines as set out in section 12.8. Safety parameters will be continuously followed-up during the duration of the trial.

9.3 Follow-up Visit

All patients will return for a post-study visit 30 +/-5 days from the time of last dose of treatment for safety and end of study assessments. For details of the schedule and nature of the assessments for this end of study visit, refer to Table 2 and section 11.2.5

10 TRIAL ASSESSMENTS

10.1 Clinical Measurements

The Investigator will ensure that all data collected in the study are provided to ICR-CTSU. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the Case Report Form (CRF) in accordance with instructions provided.

10.2 Medical History

Medical and Surgical History

Medical and surgical history, including a history of the disease being studied, other significant past and ongoing conditions should be recorded. All previous radiotherapy and chemotherapy, as well as any other therapy received for prostate cancer, must be documented with details of response and relapse dates.

Recording of Concomitant Medications

The use of or any change in the patient's concomitant medications will be recorded when the patient visits the hospital (including a review of the patient's diary card for any self-administered medication). The indication, dose, route, frequency and start and stop dates will be recorded.

Current Signs and Symptoms

Current signs and symptoms of the disease will be recorded, together with the appropriate NCI-CTC grade and causality, if appropriate.

10.3 Physical Examination

Evaluations should be performed by the same evaluator throughout the study whenever possible. A full physical examination will include the assessment of the body systems listed below and reporting if these findings were normal, abnormal or not done. A full examination will be conducted at the screening visit, cycle 1 day 1 and the end of study visit. At all other times the extent of the examination beyond vital signs and weight will be conducted as clinically indicated. Height will be recorded at screening visit only. Vital signs include blood pressure, heart rate, respiratory rate, and oral or aural body temperature.

The following must be assessed and recorded:

- General appearance
- Cardiovascular
- Respiratory
- Gastrointestinal
- Genitourinary
- Central Nervous System
- Dermatological
- Musculoskeletal
- Peripheral lymph nodes
- Other

10.4 ECG Monitoring

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the Investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. An ECG assessment will be performed at screening as a baseline assessment. Subsequent ECGs will only be performed if clinically indicated.

10.5 Brief Pain Scores

The BPI-SF will be self-administered in the clinic to the patients on the first day of each treatment cycle and the results recorded in the patient's notes (Appendix I)

10.6 Blood, Tissue and Other Sampling

Blood samples for safety assessments will be done at the local institutes. Tests relating to biomarker work on CTC, plasma and tumour material will be performed primarily at The Institute of Cancer Research Cancer Biomarkers Laboratory. Samples will be collected and processed according to specified detail in the TOPARP Laboratory Manual. There may be a requirement to send some of the samples to be processed in a different laboratory. This will be done with contractual agreements in place and patient details will remain confidential.

Bone marrow or blood cytogenetic analysis may be performed according to standard haematological practice for patients with prolonged haematological toxicities as defined in Section 3.3. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to ICR-CTSU (see section 13). Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.

Routine clinical laboratory tests will include the following;

Table 1: List of Laboratory Tests

List of Laboratory Tests		
Haematology: <ul style="list-style-type: none">• Haematocrit (Hct)• Haemoglobin (Hgb)• Platelet count with differential• Red blood cell (RBC) count• White blood cell (WBC) count	Serum Chemistry: <ul style="list-style-type: none">• Albumin (ALB)• Alkaline phosphatase (ALK-P)• Alanine aminotransferase (ALT;SGPT)• Amylase• Aspartate	Urinalysis dipstick for: <ul style="list-style-type: none">• Blood• Protein• Glucose• (Microscopic examination if abnormal)

<ul style="list-style-type: none"> • with differential • Coagulation Factors: • Prothrombin Time (PT) • Partial Thromboplastin Time (PPT) • International Normalized Ratio (INR) 	<p style="margin-left: 20px;">aminotransferase (AST;SGOT)</p> <ul style="list-style-type: none"> • Blood urea nitrogen (BUN) • Calcium (Ca) • Chloride (Cl) • Creatinine (Cr) • Glucose • Lactate dehydrogenase (LDH) • Magnesium • Phosphorus • Potassium (K) • Sodium (Na) • Total bilirubin • Total protein • Uric acid 	<p>Additional laboratory tests:</p> <ul style="list-style-type: none"> • Prostate specific antigen (PSA) • Serum testosterone • Neuron specific enolase • Chromogranins • Circulating Tumour Cells (CTCs) for enumeration & molecular characterisation • Circulating tumour DNA • Circulating tumour microRNA (miRNA) • Plasma for biomarkers • Mandatory tumour biopsy • Urine telopeptides <p>In the event of protracted myelosuppression:</p> <ul style="list-style-type: none"> • Bone marrow or blood cytogenetic analysis
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10.7 Efficacy Measurements

CT or MRI Scan Assessments (Modified RECIST)

Baseline contrast-enhanced CT of the chest, abdomen and pelvis should be performed for the assessment of measurable lesions. Where contrast is contraindicated then either an MRI of the chest, abdomen and pelvis or a non-contrast CT scan can be performed if the measurable disease is easily discernable without contrast. All baseline CT will be performed during the 28-day screening window as close as possible to Cycle 1, Day 1 of treatment. The CT scans will be repeated up to 8 days before Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3rd cycle subsequently (Table 2). CT scans may be performed earlier if clinically indicated. Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed for the purposes of the study if they were performed within the correct time frame and are of sufficient quality. Subsequent, repeat imaging requires the same method of assessment to characterise each identified lesion at baseline and during follow-up. Response categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) (refer to Appendix E) will be assigned at the scheduled visits. In the case of stable disease,

measurements must have met the stable disease criteria at least once after study start for a minimum interval of 12 weeks. PR or CR by RECIST must be confirmed with a repeat tumour assessment 4 weeks after the criteria for response was met.

For the purposes of analysis, overall response using Investigator measurements of target lesions, assessment of non-target lesions and new lesions collected on the CRF to derive the best overall response, and other protocol endpoints using these data. All medical images and tumour response assessments will be collected and retained on site as source data. A central image review may be performed by the sponsor if required.

Bone Scan Assessments

Bone scans will be used to assess bone lesions. Baseline bone scans will be performed during the 28 day screening window as close as possible to cycle 1 day 1, and up to 8 days prior to Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3rd cycle subsequently (Table 2). Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed as the baseline study if they were performed within the correct time frame and are of sufficient quality. **Bone deposits will be reported as absence or presence of new bone lesions. New lesions at the first scheduled reassessment at Week 12 must be confirmed by a second scan performed 6 or more weeks later. Disease progression by bone scan will be defined as two new bone lesions at the first 'progression' scan, confirmed by a further scan at least 6 weeks later (see section 10.9 for more details).** All medical images and tumour response assessments will be collected and archived locally. A central image review may be performed.

Diffusion weighed-MRI (DW-MRI) Scan Assessments

DW-MRI constitutes an optional component of the study. DW-MRI provides additional information regarding tumour cellularity and tumour cell death that cannot be evaluated with other imaging techniques. DW-MRI will be obtained at baseline (screening), up to 8 days prior to Cycle 3 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3 cycles subsequently. These results of these scans will not be utilized for the purpose of assigning disease status. Patients who wish to participate in this optional component of the study will be required to sign a separate Patient Informed Consent Form (PICF).

PSA Measurements

PSA will be assessed at baseline and routinely on day 1 of every 3rd cycle (12 weeks) by PCWG2 criteria (refer to Appendix D). Increases and decreases will be tracked in order to assess PSA responses. PSA changes from baseline to 12 weeks (either increment or decline) and maximal change in PSA will be recorded. Responses by PCWG2 criteria must be confirmed 28 days later.

Although serial PSA will be measured on this study and PSA progression documented by the PCWG2 criteria, the PSA value on its own is not considered a reliable measure of clinical benefit and does not correlate tightly with survival. PSA flares may occur early in the treatment and may therefore confound response assessment. Additionally, there is

emerging data that PARP-1 is implicated in multiple other essential cellular functions separate from DNA repair including *ETS* gene-mediated transcription regulation which may have a bearing on the response assessments by PSA. PSA reading should not be applied as the sole criteria to consider treatment discontinuation. In absence of evidence of radiological or clinical evidence of disease progression, patients should continue in the study despite an increment in PSA. **Overall, therefore patients will not be taken off trial purely for rising PSA levels in the absence of worsening scans and symptoms since PARP inhibitors are likely to impact tumour growth without impacting PSA secretion.**

PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG2 criteria:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA from screening (baseline) PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- For patients with PSA declines at Week 13, the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. For patients with no PSA declines at Week 13, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented, which is confirmed by a second consecutive value four or more weeks later.

CTC Conversion Rate

CTCs will be obtained at various time points before, during and after treatment for enumeration and molecular characterisation (Table 7). CTC enumeration will be performed at The Institute of Cancer Research laboratories using the analytically valid CellSearch system (Veridex, LLC). For patients with baseline CTC counts of ≥ 5 cells/7.5 ml of blood, a conversion is defined as a nadir decline in the CTC count to < 5 cells/7.5 ml of blood. The conversion of CTC counts that are ≥ 5 to < 5 and percentage decline of $\geq 30\%$ indicative of clinical benefit and improved survival outcome will be measured (76,77,78).

10.8 Safety Measurements

Safety parameters will be continuously assessed throughout the study prior to each cycle of treatment. These will include:

- Medical history, vital sign measurements, physical examination, and body weight
- Haematology, clinical chemistry, urinalysis
- Eastern Cooperative Oncology Group (ECOG) performance status
- Assessment of concomitant medications
- Adverse events (AEs) and serious adverse events (SAEs) including laboratory test AEs will be graded and summarised according to the NCI CTCAE version 4.02

10.9 Criteria For Discontinuation Of Study Treatment

The consensus guidelines of the PCWG2 recommend that confirmed radiographic progression is the most reliable indicator of clinical benefit in patients with CRPC. Based on this consideration, patients should be maintained on study treatment until confirmed radiographic progression or clinical progression or if the treating physician decides to initiate new systemic anti-cancer therapy. It is recommended that if the patient has PSA progression but no unequivocal clinical or radiological progression and an alternate treatment is not indicated, the investigators should maintain the patient's treatment until radiological disease progression is documented and confirmed. However, if the patient has unequivocal clinical progression without radiographic progression, these patients could be considered for other therapy at the discretion of the treating physician. In this circumstance, study treatment should be stopped and the patient advised regarding available treatment options. The intent of these criteria is to maintain study treatment for patients with PSA progression, given the absence of alternative treatment options available participants who have failed both castration and chemotherapy and the high likelihood that some clones of prostate cancer may be benefiting in the context of radiological stability despite a PSA rise.

A patient is considered to have progressed on study if one or more of the following findings occur:

1. Progression by bone scan:

- The first bone scan with ≥ 2 new lesions compared with baseline is observed ≤ 13 weeks from cycle 1 day 1 and is confirmed by a second bone scan taken ≥ 6 weeks later showing 2 additional new lesions (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan)
- The first bone scan with ≥ 2 new lesions compared with baseline is observed > 13 weeks from cycle 1 day 1 and the new lesions are verified on the next bone scan ≥ 6 weeks later (i.e. a total of ≥ 2 new lesions compared with baseline).

2. Progression of soft tissue /visceral disease by modified RECIST:

- A patient will be determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions by modified RECIST. **Lymph nodes have to be >2 cm in size to be deemed measurable.**

3. Unequivocal evidence of clinical progression:

A patient can be taken off study at the discretion of the treating physician under the following circumstances:

- Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumour progression even in the absence of radiological progression

- Marked deterioration in ECOG performance status to grade 3 or higher felt by the investigator to indicate clinical progression
- Felt to be in the best interest of the patient to come off study due to clinical progression

4. Death from any cause.

When study treatment is discontinued due to unequivocal clinical progression, attempts should be made to determine the patient's status at the End of Study Visit to assess for radiographic progression, including a confirmatory bone scan, as deemed appropriate by the treating team.

10.10 Withdrawal from Study

Criteria for withdrawal of study treatment are outlined below:

1. Patient Withdraws Consent

Patients have the right to withdraw from the study at any time, without prejudice to their medical care, and are not obliged to state their reasons. If the patient withdraws consent, he should be encouraged to have a complete End of Study visit and effort should be extended to clarifying the reason for the withdrawal.

Investigator may choose to withdraw a patient at any point if this is considered to be in the patient's best interest. The patient must be discontinued from the study due to any of the safety reasons outlined below:

2. Sustained or Recurrent Unacceptable Side Effects:

- Any grade 3 or 4 events that have not reverted to grade 1 or the baseline (Day 1) grade after a 42 days break off treatment with appropriate medical intervention. At the Investigator's discretion, patients may be considered for dose reductions [see Section 12.8 for management of toxicity & dose adjustments, providing they have not already undergone 2 dose reductions to 300 mg BID and 200 mg BID. If the grade 3 or 4 adverse events recurs at the lowest dose level (100 mg BID) then the patient must be discontinued].
- Unacceptable adverse events or any other toxicity in the investigator's opinion.
- Serious intercurrent illness or significant worsening of intercurrent illness that prevents further administration of treatment.
- A severe drug reaction or a hypersensitivity reaction to olaparib.

3. Non-compliance with Dosing or Trial Protocol Requirements

Patient is unable to adhere to study visit schedule or comply with protocol requirements despite several reminders about the requirements and efforts made to identify and

resolve the aetiology of the problem may be discontinued at the discretion of the Investigator.

4. Progressive Disease

Evidence of clinically significant progressive disease as defined in section 10.9.

5. Use of Prohibited Concurrent Medication

The patient will be discontinued from the protocol treatment when prohibited drug is administered. Supportive care medications are permitted with their use following institutional guidelines.

6. Other Reasons

Additionally, patients may be discontinued for any of the following reasons:

- Patient lost to follow-up
- If in the opinion of the Investigator, a change of therapy would be in the best interest of the patient
- Major protocol violation
- Incorrectly enrolled patients, i.e., the patient does not meet the required inclusion/exclusion criteria for the study

Attempts should be made to contact any patient failing to return for a scheduled visit/follow up, in order to ensure that the reason for not returning is not an adverse event. Likewise attempts should be made to establish whether any patient declaring a desire to discontinue from the study e.g. for personal reasons, is in reality due to an adverse event (AE). If the olaparib therapy is prematurely discontinued, the primary reason for discontinuation must be recorded in the appropriate section of the CRF. Patients will be required to attend a treatment discontinuation visit at least 30 +/- 5 days after discontinuing study medication for collection and/or completion of AE information. All new events occurring during this 30-day period must be recorded (if SAEs they must be reported to the ICR-CTSU within 24 hours) and followed-up to resolution, unless in the opinion of the Investigator, the condition is unlikely to resolve due to the patients' underlying disease. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the Investigator assesses as possibly related to the study medication should also be reported as an AE. The patient should return all study medication following cessation of the study.

In the unlikely event that a patient withdraws consent for further follow-up data to be collected, the appropriate form in the CRF should be completed and returned to ICR-CTSU. Clarification should be sought to ensure that the patient is not simply withdrawing from study drug. In the extremely unlikely event that the patient wishes to have their data removed from the trial completely (the implications of this should be discussed with the patient to ensure that this is their intent), this should be indicated as such on the form.

10.11 Patient Replacement Policy

An evaluable patient is defined as a patient who:

- Meets all of the inclusion and exclusion criteria specified in Sections 7.3 and 7.4 within the specified time frame;
- Has adequate histological tissue for the biomarker analysis.
- Completes twelve weeks of treatment with olaparib or experiences an event defined as treatment failure within twelve weeks.

Patients who prematurely withdraw from the study for reasons other than treatment failure may be replaced. Patients who become non-evaluable e.g. by ceasing to take LHRH agonists, may also be replaced. Replacement of ineligible and non-evaluable patients will be dependent on authorisation by the Independent Data Monitoring Committee (IDMC)

11 TRIAL ASSESSMENTS

A case report form (CRF) will be provided by ICR-CTSU for each patient eligible for the trial. The relevant forms should be completed at each hospital visit and sent to the ICR CTSU in a timely manner.

11.1 Baseline Assessments

11.1.1 Screening

Screening activities that involve imaging and collection of archival and fresh tumour tissue will be conducted within a 28-day window prior to commencing cycle 1 day 1. All other screening activities/procedures outlined below will be conducted during the screening period over 14-days prior to Cycle 1 Day 1.

- Obtain archival tissue for analysis of biomarkers (Days -28 to Day 1) Please refer to section 15, for further details of specimens to be collected.
- Obtain mandatory fresh tumour biopsy (Days -28 to Day 1). Please refer to section 15, for further details of specimens to be collected.
- Medical history including details of the following:
 - All co-morbidities
 - Oncology history / family history of cancers
 - Prior prostate cancer history including extent of disease (stage), Gleason score at diagnosis, PSA levels
 - Previous hormonal, cytotoxic, and experimental treatments with start and stop dates
- Demographics
- Listing of current baseline signs and symptoms with associated NCI Common Terminology Criteria for Adverse Events grading (0-4)

- Physical examination
- Weight, and height
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG Performance Status
- 12 lead ECG
- Laboratory tests:
 - FBC: WBC with differential count, RBC, haemoglobin, hematocrit, platelets.
 - Coagulation studies (PT/PPPT, INR)
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, random glucose, uric acid, and magnesium
 - Urinalysis: routine dipstick. Only if the dipstick is abnormal will the urine be sent for analysis
 - PSA: If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE
 - Serum testosterone
- Baseline tumour assessment
 - CT and / or other imaging procedures as clinically indicated
 - Bone Scan
 - DW-MRI (optional)
- Pain (BFI-SF) and Analgesic Usage Score
- Concomitant medications listing
 - Obtain a complete list of all prescription and nonprescription (over the counter) medications currently taken including pain medications. This also includes any nutritional supplements and/or herbal preparations.
- Assessments of adverse events
- Biomarkers
 - Circulating Tumour Cell (CTC) blood collection for enumeration and molecular characterisation
 - Circulating Plasma DNA and RNA studies
 - PAXgene mirRNA studies
 - Urine markers of bone turnover and RNA
 - Serum Proteomic studies
 - Plasma and urine metabonomic studies

11.1.2 Cycle 1 Day 1

Patients who are eligible after screening and who accept to be entered into the study should be entered within 14 days of the screening visit. All the screening assessments should have been completed and screenings results reviewed prior to the commencement of Cycle 1.

The following procedures should be carried out **prior to dosing of study treatment**:

- Update listing of current baseline signs and symptoms with associated NCI Common Terminology Criteria for Adverse Events grading (0-4)
- Updated oncology history with any events that may have transpired since screening
- Physical examination
 - Full examination
 - Vital signs including blood pressure, heart rate, respiratory rate, oral body temperature
 - Height and weight
- Assessment of ECOG Performance Status
- Laboratory Tests:
 - FBC: WBC, RBC, haemoglobin, haematocrit, platelets with differential count.
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, random glucose, uric acid.
 - Urinalysis: routine dipstick. Only if the dipstick is abnormal will the urine be sent for analysis.
 - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
- Pain (BFI-SF) and Analgesic Usage Score
- Concomitant medications listing
 - Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations
- Assessment of adverse events
- Biomarkers
 - Circulating Tumour Cell (CTC)
 - Circulating plasma DNA and RNA studies
 - PAXgene miRNA studies
 - Urine markers of bone turnover (telopeptides) and RNA
 - Serum proteomic studies
 - Plasma and urine metabonomic studies

11.2 On-treatment Assessments

11.2.1 Cycle 1 Day 8 Visit

The following assessments should be carried out on Day 8:

- Brief history and physical examination as clinically indicated
- Vital signs including blood pressure, heart rate, respiratory rate, oral body temperature
- Assessment of ECOG Performance Status

- Laboratory Tests:
 - Full blood count including WBC, haemoglobin, platelets
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, random glucose, uric acid, magnesium
- Concomitant Medications listing:
 - Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations
- Adverse events will be monitored throughout the study. At each post-baseline visit, the investigator will begin by querying for adverse events by asking each patient a general, non-directed question such as 'How have you been feeling since the last visit?' Directed questioning and examination will then be done as appropriate.
- Dosing compliance check
- Obtain post treatment mandatory fresh tumour tissue biopsy (Cycle 1 Days 8 to Day 28)
- Biomarkers
 - Circulating Tumour Cells (CTC)
 - Plasma and urine for metabolomic studies

11.2.2 Cycle 1 Day 15 Visit

- Biomarkers
 - Circulating Tumour Cells (CTC)

11.2.3 Day 1 of Cycles 2, 3, 5, 6, 8, 9, 11, and 12 (Continue every cycle beyond Cycle 12)

The following assessments should be carried out at the indicated time point:

- Brief history and physical examination as clinically
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Weight
- Assessment of ECOG Performance Status
- Concomitant Medications listing
 - Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations.
- AE evaluation and recording at each post-baseline visit
- PSA measurements will be conducted every 12 weeks. PSA results will be assessed according to PCWG2 criteria

- Dosing compliance check and a count of study medication will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not 100% in the absence of toxicity, patient should be re-instructed regarding proper dosing procedures
- Pain (BFI-SF) and Analgesic Usage Score (each cycle)
- Laboratory Tests:
 - FBC: WBC, RBC, haemoglobin, haematocrit, platelets with differential count
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, random glucose, LDH, uric acid, magnesium
- Biomarkers
 - CTC collection (Cycles 2, 3, 4, 7, every 3rd cycle thereafter and at treatment discontinuation/EOS)
 - Plasma for DNA, RNA studies (Cycles 2, 3, 5 and at treatment discontinuation/EOS)
 - Paxgene miRNA studies (cycle 3, 5 and at treatment discontinuation/ EOS)
 - Urine and plasma metabolomic (cycles 2, 3 ,6 and at treatment discontinuation/EOS)
 - Urine markers of bone turnover and RNA (cycle 3, cycle 6 and at treatment discontinuation/ EOS)

11.2.4 Cycles 4, 7, and 10 and Treatment Discontinuation Visit (continue every 3rd cycle beyond Cycle 10)

In preparation for the study visit, the following assessments should be conducted up to 8 days prior to the indicated visit. Results should be available for review at the Cycle 4, 7, or 10 Day-1 visit and every 3rd cycle beyond Cycle 10.

- CT Scan
- Bone Scan
- DW-MRI (optional)
- Other imaging procedures should be conducted as clinically indicated

At the study visit the following assessments should be conducted:

- Brief history and physical examination as clinically indicated
- Vital signs including blood pressure, heart rate, respiratory rate and oral body temperature.
- Weight
- Assessment of ECOG Performance Status
- Laboratory Tests
 - FBC: WBC, RBC, haemoglobin, platelets with differential count, chemistry with electrolytes: sodium, potassium, chloride, carbon dioxide, creatinine, BUN, AST,

ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, glucose, LDH, uric acid, magnesium, random glucose.

- PSA (every 12 weeks): If patient undergoes a DRE, then PSA must be sampled prior to the DRE
- Concomitant medications listing
- AE evaluation and recording
- Dosing compliance check
- Pain (BFI-SF) and Analgesic Usage Score (each cycle)
- Review of imaging results (CT and bone scan) should be conducted and disease response /progression ascribed at the actual study visit (Cycle 4, 7, or 10 Day 1) unless otherwise indicated.
- Tumour biopsy (this end of study biopsy is optional and can be collected at any point from treatment discontinuation up to the end of study visit).
- Biomarkers
 - CTC collection (Cycles 2, 3, 4, 7, every 3rd cycle thereafter and at treatment discontinuation/EOS)
 - Plasma for DNA, RNA studies (Cycles 2, 3, 5 and at treatment discontinuation/EOS)
 - Paxgene mirRNA studies (cycle 3, 5 and at treatment discontinuation/EOS)
 - Urine and plasma metabolomic (cycles 2, 3, 6 and at treatment discontinuation/EOS)
 - Urine markers of bone turnover and RNA (cycles 3, 6 and at treatment discontinuation/EOS)
 - Serum proteomic studies (at treatment discontinuation/EOS)

11.2.5 End-of-Study Visit

The following safety assessments should be carried out at the End-of-Study participation when patients are off study or terminate trial participation early:

- Physical examination and weight
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature.
- Assessment of ECOG Performance Status
- 12-lead ECG is not mandated but should be done if clinically indicated
- Laboratory tests:
 - FBC: WBC, haemoglobin, platelets with differential count
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphorus, random glucose, LDH, uric acid, magnesium.
 - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
 - Disease Progression Assessment Review of imaging (CT, Bone scan, DW-MRI)

- results assessment according to modified RECIST and PCWG22 criteria.
 - Review of PSA results conducted over the course of the study and PSA progression assessment according to PCWG2 criteria
- Concomitant medications listing: update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations.
- Adverse events
 - AE follow-up to determine if any new or ongoing drug-related AE or any SAE regardless of relationship to study drug exists is required for 30 days post last dose or until patient receives anticancer therapy, whichever comes first
- Final dosing compliance check if not performed at the Treatment Discontinuation visit.
- Pain (BFI-SF) and Analgesic Usage Score
- Biomarkers
 - Circulating CTC collection (EOS if not obtained at treatment discontinuation)
 - Circulating plasma for DNA, RNA studies (EOS if not obtained at treatment discontinuation)
 - Paxgene mirRNA studies (EOS if not obtained at treatment discontinuation)
 - Urine and plasma metabolomic studies (EOS if not obtained at treatment discontinuation)
 - Urine markers of bone turnover and RNA (EOS if not obtained at treatment discontinuation)
 - Serum proteomic studies (EOS if not obtained at treatment discontinuation)

11.2.6 Safety follow up (30 days after treatment discontinuation)

Patients who discontinue treatment will be followed for safety outcomes until 30 days +/- 5 following the patient's last dose or until the patient receives another anti-cancer therapy, whichever occurs first. Once a patient has completed the study, progressed or started another anticancer therapy, follow-up data will be obtained at the end of study visit and if necessarily by a telephone interview. PSA kinetics and rate of disease progression data after drug discontinuation will be captured when possible.

11.3 Unscheduled Visits

Unscheduled visits and procedures may be conducted at the investigator's discretion for the safety follow-up of the patient. Such visits and procedures must be fully recorded in source documents regarding the purpose and outcome of the visit/assessment.

11.4 Early Discontinuation

Patients will be advised in the written informed consent form that they have the right to withdraw from study drug treatment at any time without prejudice, or may be withdrawn at

any time at the discretion of the investigator or the sponsor. Notification of early patient discontinuation from the study and the reason for discontinuation will be made on the protocol deviation form provided. Patients removed from therapy for any reason should continue to be followed for the collection of safety data as outlined in the Safety Follow-Up visit procedures. For patients who refuse or are unable to attend further clinic study visits, telephone contact should be attempted to follow up for adverse events 30 days \pm 5 days after the last dose of study drug. All serious adverse events will be followed until resolution, until the event has stabilised and/or become chronic, until it has been determined that the event was caused by aetiology other than the study drug, or through 30 days, whichever comes first. Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete study-related assessments and retrieve any outstanding data and study drug. Such efforts should be documented in the source documents.

Table 2: Schedule of Procedures and Clinic Visits

Procedures & Assessments	Screening	Cycle 1	Cycle 1	Cycle 1	Cycle 2, 3, 5, 6, 8, 9, 11, 12	Cycle 4, 7,10, every 3 rd cycle	Cycle 4, 7 ,10, and every 3 rd cycle	End of Study
Activity day	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 1	Up to 8 days before	Day 1	
Informed Consent ¹	X							
Medical History ²	X							
Obtain Archival Tissue ³	X							
Tumour Biopsy ⁴	X		X(8± 21 days)					X (optional)
Assessment of Symptoms ⁵	X	X	X		X		X	X
Dosing compliance ⁵			X		X(every cycle)		X	
Concomitant medication ⁵	X	X	X		X		X	X
Adverse events ⁵	X	X	X		X		X	X
Physical Examination & Vitals ⁶	X	X		X	X		X	X
Complete Pain Questionnaire ⁷	X	X			X(every cycle)		X(every cycle)	X
12 Lead ECG ⁸	X							
Safety Bloods ⁹	X	X	X		X		X	X
Testosterone Level ¹⁰	X							
PSA Levels ¹¹	X	X					X (C4,7, 10 & every 12 weeks thereafter)	X
Neuron specific enolase / chromogranins ¹²	X							
Imaging Assessments								
Bone Scan ¹²	X					X		
DW-MRI (optional) ¹⁴	X					X		
CT Scan ¹⁵	X					X		
Disease Progression Assessment ¹⁶	X						X	X
Blood and Urine Biomarker Tests								
Plasma DNA & RNA ¹⁷	X	X			X (C2,3,5)			X
Circulating Tumour Cells ¹⁸	X	X	X	X	X (C2, 3)		X	X
Blood miRNA ¹⁹	X	X			X (C3,5)			X
Plasma Proteomics ²¹	X	X						X
Plasma and urine Metabolomic ²¹	X	X			X (C2,3,6)			X
Markers of Bone Turnover and RNA ²²	X	X			X(C3,6)			X

Procedures and Clinic Visits

1. Written informed consent must be obtained within 28 days period prior to Cycle 1 Day 1.
2. Medical history at screening will detail demographic, family history, co-morbidities, prior treatments for prostate cancer and baseline adverse events.
3. Archival tumour tissue will be obtained for molecular characterisation. Patients who do not have archival tumour tissue will be required to have a repeat tumour biopsy in order to obtain the required tumour tissue for molecular characterisation.
4. Fresh tumour biopsies are a mandatory component of this study and will be obtained prior to commencing treatment (during the screening period) and post treatment (at any point from Day 8 to Day 28 of Cycle 1). The third biopsy at the time of treatment discontinuation is optional.
5. At each clinic review, symptoms, concomitant medication, treatment compliance and adverse events will be assessed. Adverse events will be assigned a grade according to the CTCAE version 4.02 and causality. Adverse Event follow-up is required for 30 +/-5 days post last dose of treatment to determine if any new or ongoing drug related AE or any SAE regardless of relationship to drug persists.
6. Includes physical examination, blood pressure, heart rate, respiratory rate, oral body temperature, and weight. Height will only be measured at the screening visit. A full physical examination will be performed at screening, Cycle 1 Day 1 and at the EOS visit. At all other clinic reviews physical examinations will be performed as clinically indicated.
7. A Brief Pain Inventory Questionnaire will be given to the patient to fill in at screening and at the beginning of each cycle. The Brief Pain Inventory Score will be annotated in the patients CRF.
8. ECG will only be performed at the screening visit. ECGs should be obtained with the subject in the supine resting position for several minutes. Abnormal ECG related to electrolyte abnormalities should be repeated following the correction of the electrolyte abnormalities. ECGs will only be repeated beyond screening if clinically indicated.
9. A full array of safety bloods including the full blood count, blood chemistry, liver function test, clotting profile, glucose, amylase, etc. will be obtained and checked at the beginning of each cycle of treatment.
10. Serum testosterone level will be checked during the screening period to ensure a systemically castrate state [testosterone levels of < 50 ng/dL (< 2.0 nM)]. Testing for serum testosterone, PSA and routine safety bloods will be performed at the local site laboratory.
11. PSA testing will be done at screening and every 12 weeks while on treatment. PSA responses by PCWG2 criteria will need to be confirmed 4 or more weeks later.
12. Neuron specific enolase and chromogranins A and B to be performed in patients with baseline PSA<10.
13. A bone scan will be obtained at baseline and after every 3rd cycle of treatment. New bone deposits will need to be confirmed with a repeat bone scan 6 or more weeks later.
14. DW-MRI is optional and will be performed at baseline (screening) and every 12 weeks thereafter.
15. CT scan will be obtained at baseline and after every 3 cycles of treatment. If a status of partial or complete response is made, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.
16. Disease progress assessment will be made after every 3rd cycle of treatment at the clinic visits.
17. Serum plasma for circulating plasma DNA and RNA will be collected in BD Vacutainer® CPT™ tubes (3x10mls) at screening, C1D1, C2,D1, C3,D1, C5D1 and at either termination of treatment or EOS.
18. Blood for CTC analysis should be collected at the indicated time points in 2 Cell Save™ tubes (10mL each, Veridex, PA). Patients being enrolled at Royal Marsden Hospital NHS Trusts will have an additional 1 CTC blood samples (i.e. in total 3 CTC blood samples) collected at screening and Cycle 1 Day 1 and subsequently 2 tubes at all other time points.
19. Blood samples for whole blood miRNA analysis will be collected in a 2.5ml PAXgene Blood RNA Tube at screening, Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1 and at either termination of treatment or EOS visit.
20. Blood samples (1x10mls) will be collected for PTEN proteomics profiling at screening and Cycle 1 Day1.
21. Urine and plasma metabolomic profiles will be evaluated both at baseline and during treatment. These blood samples will be collected in a 6ml BD vacutainer with heparin.
22. A 24 hour urine sample will be obtained at screening, C1D1,C3D1, C6D1 and at study termination or EOS to assess markers of bone turnover such as telopeptides.

12 TRIAL TREATMENT

12.1 Drug Manufacturer

Olaparib tablets will be manufactured and provided free of charge by AstraZeneca to participating centres. AstraZeneca will manufacture to Good Manufacturing Practice (GMP) and UK Legislation.

12.2 Presentation / Formulation of Olaparib

Olaparib is presented for oral administration as a green, oval bi-convex film-coated tablet containing 100 mg of drug substance.

12.3 Drug, Dose and Schedule

The dose of 400 mg olaparib, twice daily orally, continuous dosing has been selected for this protocol based on the pharmacokinetic (PK), pharmacodynamic (PD) and clinical efficacy data from the Phase I-II studies including an ongoing bioavailability study (10, 11, 49, 50, 61, 62). The olaparib dose should NOT be adjusted according to the patient's body weight, even for very heavy or light patients. Patients will be given sufficient supplies for 1 cycle (28 days+2) of treatment.

12.4 Instructions for Administration of Olaparib

Patients should swallow the olaparib tablets whole with a glass of water in the morning and evening at the same times each day to ensure a dose interval of approximately 12 hours. Olaparib must be administered no sooner than 1 hour after food and the patient should then refrain from eating for a further 2 hours post dose to avoid the potential effect of food on drug absorption. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. If vomiting occurs shortly after the olaparib is swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the trial miss a scheduled dose for whatever reason (e.g. as a result of forgetting to take the dose of olaparib), he will be allowed to take the scheduled dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

12.5 Olaparib Treatment Compliance

A member of the Investigative site's study team will query the patient for treatment compliance at day 1 of each new cycle of treatment. All patients must return their bottle of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Compliance will be assessed by capsule count and questioning by the study nurse and the information will be recorded.

12.6 Duration of Therapy

Patients may continue with olaparib treatment as long as they remain free from intolerable toxicity, in the Investigator's opinion, are receiving clinical benefit and do not meet any discontinuation criteria (see Section 10.9 for discontinuation criteria).

12.7 Supportive Care Guidelines

Based upon experience from Phase I and II studies, olaparib is generally well tolerated. The safety concerns are primarily related to the risk of myelosuppression. Supportive care should be provided therapeutically and prophylactically as deemed necessary by the treating physician including but not limited to the items outlined below:

Gastrointestinal symptoms

Prophylactic anti-emetics and/or anti-diarrhoeals will not routinely be given. Should a patient develop nausea, vomiting and/or diarrhoea that, in the Investigator's opinion, is considered to be related to olaparib, then appropriate prophylactic treatment may be initiated. Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

Myelosuppression

Routine prophylaxis with granulocyte colony-stimulating factor (G-CSF)/granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin is not recommended. Nevertheless, use is permitted at the Investigator's discretion and according to local hospital guidelines. The occurrence of leukopenia and/or anaemia should be managed as deemed appropriate by the investigator. The use of growth factors must be discontinued once the AE has recovered to CTCAE grade 1 or better. They may be resumed, if necessary, if leukopenia/anaemia develops again and discontinued once it recovers. The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the CRF. Checking haematinics levels (Iron, B12 and folate) and providing supplementation if these are found to be low is advocated. Transfusions may be given as clinically indicated for the treatment of anaemia and thrombocytopenia.

Symptoms Related to Castration

Treatment with androgens, estrogens and progestin to control hot flashes is not allowed. Antidepressants that do not interfere with P450 enzyme function are permitted for the management of hot flashes. Long-term androgen deprivation may lead to metabolic diseases, such as glucose intolerance, hypercholesterolemia, and osteoporosis, appropriate medication may be prescribed to manage these conditions. All such AEs need to be recorded.

12.8 Guidelines for Management of Toxicity and Dose- Modification

Based on Phase I and Phase II studies, olaparib is generally well tolerated. Safety concerns are mainly related to the possibility of myelosuppression.

Any toxicity observed during the course of the study may be managed by a dose interruption if deemed appropriate by the Investigator. Treatment must be interrupted if any clinically significant NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of olaparib.

Repeat dose interruptions are allowed as required, for a maximum of 42 days on each occasion. Olaparib must be interrupted until the patient recovers completely or the toxicity reverts to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.02) grade 1 or less. When the toxicity is appropriately resolved, the patient can resume treatment with olaparib with a dose reduction according to Table 3 if a treatment break of ≥ 14 days was required for the resolution of the toxicity. If the event recurs with the same severity following olaparib re-challenge, treatment should be interrupted again, and on resolution, a further dose reduction made. A maximum of 3 dose reductions will be allowed. Regular 7-day drug holidays will also be permitted if myelosuppression is an issue at these doses.

If, on re-starting treatment following 3 dose reductions, the event continues to occur at the same severity, treatment should be discontinued and the patient withdrawn from study. If the toxicity has not resolved to at least grade 1 during the maximum 42-day period, and/or the patient has already undergone a maximum of 3 dose reductions already, the patient must permanently discontinue treatment with olaparib. Once the dose of olaparib has been reduced under no account should it be re-escalated.

The dose of olaparib should not be reduced for grade 3-4 gastrointestinal adverse events that have not been adequately managed with appropriate prophylactic measures. In all cases where the olaparib dose has been interrupted or the patient discontinued due to unusual or unusually severe toxicity considered related to olaparib, the Investigator must contact the Chief Investigator and CTSU trial management team. All dose modifications and interruptions (including any missed doses), and the reasons for the modifications/interruptions are to be recorded in the CRF.

Olaparib should be temporarily withheld in the event of:

- Grade 4 neutropenia
- Grade 2-4 neutropenia with infection
- Platelet count lower than $50 \times 10^9/L$
- Non-haematological toxicity grade 3 or greater, except nausea, vomiting or diarrhoea and fatigue associated with suboptimal pre-medication and/or management OR transient and clinically insignificant biochemical blood results.
- Aspartate transaminase (AST) or alanine transaminase (ALT) elevations grade 3 or higher for more than 7 days.
- New or worsening pulmonary symptoms or radiological abnormality occurs which are suggestive of pneumonitis

- Any other toxicity that, in the view of the principal investigator and the medical monitor, represents a clinically significant hazard to the patient until resolution of toxicity to no more than grade 1.

Standard Dose	Olaparib Dose
First dose reduction due to NCI-CTC grade 3 or 4 treatment-related Serious Adverse Events / Adverse Events (excluding inadequately managed gastrointestinal symptoms)	300 mg BID
Recurrent episode of NCI-CTC grade 3 or 4 event despite one previous dose reduction (excluding inadequately managed gastrointestinal symptoms)	200 mg BID
Recurrent episode of NCI-CTC grade 3 or 4 event despite two previous dose reductions(excluding inadequately managed gastrointestinal symptoms)	100mg BID

Table 3: Summary Guidelines for Dose Reductions

Management of prolonged haematological toxicities including anaemia, neutropenia or thrombocytopenia whilst on study treatment

If any study treatment is interrupted/delayed because of one or more of the following:

- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 neutropenia
- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 thrombocytopenia
- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 anaemia and or development of blood transfusion dependence

Weekly blood counts should be performed during the study treatment interruption/delay. If the levels have still not recovered to CTC Grade ≤ 1 after 42 days of dose interruption, the patient should be referred to a haematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Bone Marrow or blood cytogenetic analysis:

If a bone marrow analysis is carried out to evaluate cytopenia it should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Development of myelodysplastic syndrome should be reported as an SAE and full reports must be provided by the Investigator for documentation on the Patient Safety database. If a bone marrow or blood cytogenetic and flow cytometry is conducted the presence or absence of abnormalities (YES/NO) will be documented for cytogenetics and flow cytometry on the clinical database.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Chief Investigator and CTSU trial management team. All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded.

12.9 Packaging and Labelling

AstraZeneca have employed Fisher Clinical Services to coordinate IMP packaging, labelling and distribution for this trial. Olaparib will be supplied in High Density Polyethylene containers containing desiccant. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence. Olaparib will be provided to each site in labelled bottles. Each bottle will have a label permanently affixed to the outside and will be labelled in accordance with Good Manufacturing Practice and local regulations, stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. Labels will refer to Olaparib as AZD2281 and will include blank lines for quantity of tablets to be taken, patient trial ID and date of dispensing.

12.10 Drug Storage

Drug Storage by Pharmacy

All study medication must be kept in a secure place under appropriate storage conditions (at temperatures less than 30°C and protected from light). Study medication should not be stored under refrigerated conditions. Additional information is provided in the olaparib Investigator's Brochure. Any deviations from the recommended storage conditions should be immediately reported to the sponsor and the use of olaparib interrupted until authorisation for its continued use has been given by AstraZeneca and the sponsor.

Storage Requirements for the Patient

Olaparib must be stored in the bottle with the cap tightly on at room temperature. Study medication should not be refrigerated. Patients should be advised to keep all medication out of the sight and reach of young children.

12.11 Distribution of Drugs to Site

No drug will be distributed to participating centres unless ICR-CTSU is satisfied that the required approvals, agreements and initiation procedures are complete.

Participating pharmacy departments should contact Fisher Clinical Services via the ICR-CTSU trial management team to request drug supplies following patient registration.

Records must be kept for all deliveries and a copy of the order / delivery note placed in the Site Pharmacy File and kept within the pharmacy department as in routine practice. At the end of the trial, it must be possible to reconcile supply and usage of all stock. Account must be given to any discrepancies and certificates of delivery and return must be signed.

12.12 Pharmacy Responsibilities and Drug Accountability

Labelling:

Labelling will be the responsibility of Fisher Clinical Services and will be compliant with Annex 13 of the Good Manufacturing Guidelines (GMP) and all applicable local regulatory requirement. Each hospital pharmacist must also insert the name of the Principal Investigator (PI) or hospital specific code by which the PI can be identified, together with the Trial ID and patient's name,.

The local pharmacy department must designate a responsible person for ensuring that:

- The study drug is handled and stored safely and properly
- The study drug is labelled for each patient in accordance with Annex 13 of the EU Good Manufacturing Practice (GMP) Guidelines
- The study drug is dispensed only to trial patients and in accordance with the protocol and under the guidelines of the site's dispensing standard operating procedure
- Full accountability is maintained for the study drug
- Patients should be instructed to return unused olaparib, preferably in their original packs. Olaparib which has been dispensed to a patient and returned unused must not be re dispensed to a different patient
- There is a sufficient supply of study drug for patients' continued treatment, and in a timely manner, contact ICR-CTSU for re-supply of stock
- Study drug expiry dates are monitored and are used in order of expiry date order i.e. earliest expiry first
- All unused drugs will be accounted for and retained until advised otherwise. Unused and returned study drug may be destroyed locally in accordance with hospital protocol and following written instructions from the sponsor

Patient cards

Small wallet sized cards will be produced by ICR-CTSU on request by the participating centre. Each card will state:

- the name of the participating centre
- that the patient is participating in the TOPARP trial
- that the patient is taking olaparib

12.13 Concurrent Medications

The concurrent administration of other anticancer therapies, including cytotoxic, hormonal (except LHRH analogues) or immunotherapy, is prohibited during study treatment. The use of any natural/herbal products or other “folk remedies” should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded.

Olaparib is an investigational drug for which no data on *in vivo* interactions are currently available. Based on *in vitro* data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. *In vitro* data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib. Whilst this is not an exhaustive list of inhibitors, it covers the known potent inhibitors which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfonavir

For patients taking any of the above, the required wash-out periods prior to starting olaparib is one week.

In addition, to avoid potential reductions in exposure due to drug interactions, the exclusion of the following P450 inducers is recommended:

- Phenytoin, rifampicin, carbamazepine and phenobarbitone, nevirapine, modafinil and St John’s Wort (*Hypericum perforatum*)
- For patients taking any of the above, the required wash-out periods prior to commencing olaparib are:
- Phenobarbitone - 5 weeks; any of the others - 3 weeks.

If use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient’s safety and welfare, the Investigator must contact the ICR-CTSU and a decision to

allow the patient to be enrolled in the study will be made on a case-by-case basis by the Chief Investigator.

If at any time an investigator suspects a drug-drug interaction due to olaparib, an AE report should be completed and the study sponsor informed.

Permitted Concomitant Therapy

- Leuteinizing hormone-releasing hormone (LHRH) agonists to maintain a testosterone level <50g/dL should be administered in patients who have not undergone an orchidectomy.
- Conventional multi-vitamins and minerals.
- Stable chronic non-immunosuppressive systemic doses of corticosteroids up to a dose of prednisolone 5mg BID or equivalent so long as the treatment was initiated prior to commencing the trial medication with evidence of progression on the dose of steroids. Higher doses of steroids are permitted if clinically indicated for acute medical conditions.
- Initiating bisphosphonate therapy or adjusting bisphosphonate dose/regimen within 30 days prior to Cycle 1 Day 1 is prohibited. Patients on a stable bisphosphonate regimen are eligible and may continue.
- Anticoagulant Therapy: Patients who are taking warfarin may participate in this trial however, it is recommended that prothrombin time (International Normalised Ratio [INR] and activated partial thromboplastin time [APTT]) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted and is preferable given the potential for myelosuppression.
- **Palliative radiotherapy:** may be used for treatment of pain at the site of bony metastases that were present at baseline, providing the Investigator does not feel that this is an indication for the patient to come off treatment due to disease progression. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the CRF.

Therapy considered necessary for the subject's welfare and which is believed not to interfere with the study medication may be given at the discretion of the investigator. If concurrent medications may have an effect on study outcomes, a statement to the effect that these medications should be administered in dosages that remain constant throughout the course of the trial should be included. All medications (prescriptions or over-the-counter medications), the reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records..

13 PHARMACOVIGILANCE

13.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a study drug, whether or not considered related to the study drug. Signs and symptoms of metastatic disease, as determined by the local clinical investigator, are not adverse events.

Adverse Reaction (AR): all untoward and unintended responses to the study drug related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions i.e. an AR is possibly, probably or definitely related to the study drug. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR): Any untoward medical occurrence or effect which occurs within 30 days of the patient receiving study drug that at any dose:

- **results in death:** the patient's death is suspected as being a direct outcome of the AE.
- **is life-threatening:** refers to an event in which the subject was at risk of death at the time of the event. It also refers to an event that would result in death with the continued use of the product; it does not refer to an event which hypothetically might have caused death if it were more severe.
- **requires hospitalisation, or prolongation of existing inpatient hospitalisation:** admission to hospital overnight or prolongation of a stay in hospital was necessary as a result of the AE..
- **results in persistent or significant disability or incapacity:** the AE results in a significant or persistent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- **results in a congenital anomaly or birth defect**

Hospitalisation meeting the definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Inpatient admission does not include: rehabilitation facilities, hospice facilities, skilled nursing facilities, nursing homes, routine emergency room admissions, same day surgeries (as outpatient/same day/ambulatory procedures), or social admission (e.g., subject has no place to sleep). Outpatient treatment in an emergency room is not itself an SAE, although the reasons for it may be. Hospital admissions/surgical procedures planned for a pre-existing condition

before a patient is randomised to the study are not considered SAEs, unless the illness/disease deteriorates in an unexpected way during the study

Medical judgement should be exercised in deciding whether other AE/ARs are serious. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious

N.B. progressive disease and death due to disease are not considered SAEs but should be reported on the relevant forms.

Suspected Unexpected Serious Adverse Reaction (SUSAR): Any serious adverse event with a suspected relationship to study drug that is not listed on the Investigator Brochure (IB) and in the opinion of the Chief Investigator, is unexpected.

13.2 Clinical & Laboratory Adverse Events

AEs Based on Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

AEs Based on Examinations & Laboratory Tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfil any of the SAE criteria or are the reason for stopping treatment with the investigational product. If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator should use the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms.
- Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting as an AE).
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy.

- Test result leads to any of the outcomes included in the definition of a SAE.
- Test result is considered to be an adverse event by the investigator or sponsor.
- Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for bullet point 4.
- Clinically significant laboratory results must be recorded in the patient's CRF.

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the sponsor (or his/her designated representative), or until a diagnosis that explains them is made.

13.3 Causality

Many adverse events that occur in this trial, whether they are serious or not, will be known treatment related toxicities. The Principal Investigator is responsible for the assessment of causality of serious adverse events (see definitions of causality table).

If there is any doubt about the causality of an event, the investigator should inform ICR-CTSU who will notify the Chief Investigator. The drug manufacturer and/or other clinicians may also be asked for advice.

13.4 Severity of Adverse and Serious Adverse Events

Adverse event (AE) severity is a clinical determination of the intensity of an AE and SAEs. The severity assessment for a clinical AE should be completed using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.02). Any AE not listed in the CTCAE will be graded as follows:

Table 4: Severity of Event

Grade	Definition	Description
1	Mild adverse event	Does not interfere with the patient's usual function [awareness of symptoms or signs, but easily tolerated (acceptable)].
2	Moderate adverse event	Interferes to some extent with the patient's usual function [enough discomfort to interfere with the usual activity (disturbing)].
3	Severe and undesirable adverse event	Interferes significantly with the patient's usual function [incapacity to work or to do usual activities (unacceptable)].
4	Life-threatening or disabling adverse event	Results in risk of death, organ damage or permanent disability (unacceptable).

5	Death related to adverse event. Relationship to Study Drug	Event has a fatal outcome.
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Causality of Event

A determination should be made by the investigator regarding the relationship (if any) between an AE and the study drug. A causal relationship is present if there is a reasonable possibility that the AE may have been caused by the study drug. The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study.

Table 5: Definitions for Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient’s clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

The expectedness of a SAR related to the study drug should be assessed by the Chief Investigator in accordance with the information provided in the IB for olaparib.

Expected SARs should be reported as per the SAE reporting guidelines. SAEs should be reported up to 30 days after the patient's last dose of study medication

A summary of ‘expected’ adverse reactions as stated in the IB is listed below:

Table 6: Expected Adverse Reactions (Olaparib Monotherapy)

Frequency of Adverse Events	Very common	Common	Rare
Grade (G)	Mild to moderate CTCAE:G1-2	Mild to moderate CTCAE:G1-2	Mild to moderate CTCAE:G1-2

Adverse Events	Nausea	Anaemia	Lymphopenia
	Vomiting	Headache	Tachycardia
	Fatigue	Dyspepsia	Thrombocytopenia
		Dizziness	Neutropenia
		Asthenia	
		Decreased appetite	
		Dysgeusia	
		Constipation	

13.5 Procedures for Recording and Reporting Adverse Events

13.5.1 Reporting Serious Adverse Events (SAEs) to ICR-CTSUS

Any SAE that occurs from the time of screening and up to 30 days following the last dose of olaparib must be reported, whether or not considered causally related to the study treatment.

All SAEs should be reported to ICR-CTSUS, within 24 hours of the study team becoming aware of the event, by completing the trial specific SAE forms and faxing to:

The ICR-CTSUS safety desk
Fax no: 0208 722 4368
For the attention of the TOPARP Trial team

Investigators or other site personnel must ensure that:

- All SAE forms must be completed, signed and dated by the Principal Investigator or designated representative.
- All SAE reports are supported by documentation in the patient's medical records. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
- All patients with a serious adverse event must be followed up and the outcomes reported in a follow up severe adverse event report form to the ICR CTSUS.
- In the event of a fatal or life-threatening AEs where important or relevant information is missing, active follow-up must undertaken immediately.

13.6 Review of Serious Adverse Events (SAEs) or Reactions (SARs)

Reported events / reactions using the SAE forms will be assessed by the Chief Investigator (or designated representative) for causality and expectedness.

NB. The Chief Investigator cannot down grade the Principal Investigator's assessment of causality.

SAEs assessed as having a causal relationship to study drug and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities by ICR-CTSU (see figure 4 for SAE reporting).

Centres should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of the SAE.

13.7 Expedited Reporting of SUSARs

If an SAE is identified as being a SUSAR by the Chief Investigator, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Main REC, the sponsor institutions and AstraZeneca within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the Chief Investigator, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Main REC, the sponsor institutions and AstraZeneca within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA, Main REC, the sponsor institutions and AstraZeneca as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

The Principal Investigators at all actively recruiting centres will be informed of any SUSARs occurring within the trial at regular intervals.

13.8 Follow up of Serious Adverse Events

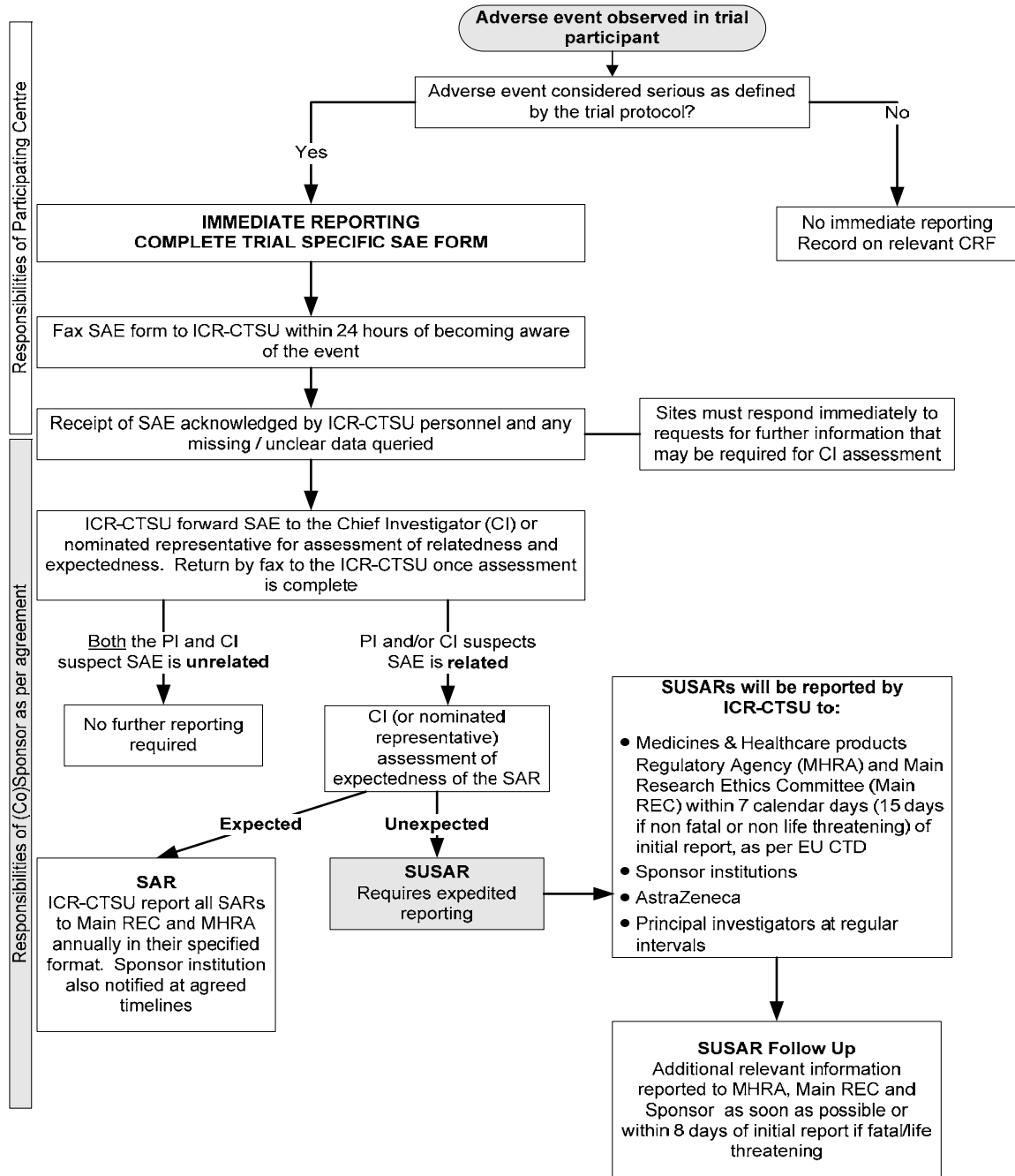
Centres should continue to follow up SAEs until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Information on outcome of the SAE should be completed on the relevant part of the original SAE and faxed to ICR-CTSU as soon as the Principal Investigator becomes aware.

NB Any male patient who fathers a child whilst on study medication, must be followed up and the outcome reported to ICR-CTSU who will then forward the details to AstraZeneca.

13.9 Annual Reporting of Serious Adverse Reactions

An annual report will be provided to the MHRA and the Main REC, by ICR-CTSU and copied to the Co-sponsors, on the anniversary of the date when the Clinical Trials Authorisation (CTA) was obtained. This will include all related events reported on SAE forms, and a report from the Independent Data Monitoring Committee (IDMC).

Figure 4: Flow diagram for SAE reporting, and action following report



NB. All SAE's should continue to be followed up as specified in the protocol.

14 STATISTICAL CONSIDERATIONS

14.1 Trial Design

The aim of this design is to look for potentially sensitive subgroups of patients by undertaking a screening trial (part A) followed by a validation trial (part B) if there is evidence a sensitive subgroup exists.

Both of these trials are non-randomised with response rate being assessed at 6 months post registration as the primary endpoint. These trials will be followed by a randomised phase II trial (part C) in the sensitive patient groups with overall survival as the primary endpoint. The aim is to identify a sensitive subgroup with a 50% response rate on the basis that high response rates are necessary to be confident of demonstrating a survival benefit, the primary goal of the phase II strategy.

It is possible that all patients are sensitive to treatment in which case it has to be possible to apply the same efficacy and inefficacy criteria as are used in the validation trial to all patients in the screening trial.

Part A

The screening trial will involve all comers (unselected patients) and is an open-labelled, multi-centre two-stage design based on $H_0: p_0=0.05$; $H_a: p_1=0.20$; $\alpha=0.02$ and $\beta=0.10$. It will recruit a **maximum of 45 patients** (30 in stage 1 and 15 in stage 2) with an initial efficacy level of 20% and an inefficacy level of 5%, to allow for the fact that only a small subset of patients may be sensitive to olaparib.

This part will evaluate the anti-tumour activity of olaparib in unselected CRPC patients and will identify potential biomarkers of response.

- **Stage 1**

The first stage will enrol 30 patients and when all 30 have been followed up for a minimum of 6 months an interim analysis will take place to evaluate the response rate:

Given the efficacy level of 20% and inefficacy level of 5% the trial will be terminated with the conclusion of inefficacy if there are **2 or fewer responses**. If there are **15 or more responses** in the first stage, broad efficacy will be concluded and no more patients will be entered and Part C will commence in unselected patients.

If between **3 to 14 patients respond**, patient accrual will continue to a total of 45 patients (stage 2) and an investigation into the identification of a potential biomarker of response will be carried out.

- **Stage 2**

If the trial progresses to stage 2, a further 15 patients will be recruited, giving a total of 45 patients for part A. An interim analysis will be triggered once 45 patients have been followed up for a minimum of 6 months or alternatively we observe 23 or more responses. The recruitment will be halted.

If **23 or more** patients respond, Part C will be initiated. If **5 or fewer patients** respond, the null hypothesis will be accepted and the study will be terminated. If **between 6 and 22 patients respond**, an investigation into the identification of potential biomarkers of response will be carried out. If a potential biomarker subgroup is found, Part B will be undertaken. If a subgroup is not found, then Part C will be undertaken if at least 19 of the patients have responded, otherwise the study will be terminated since sufficient activity has not been observed based on $H_0: p_0=0.3$; $H_a: p_1=0.5$; $\alpha=0.059$ and $\beta=0.11$.

Deriving a classifier for identification of tumours with high susceptibility to PARPi olaparib in CRPC.

All patients participating in this trial will have their archival tissue, fresh tumour biopsies and circulating tumour cells collected prior to starting olaparib. The primary biomarkers to be evaluated include PTEN loss by IHC and FISH, *ETS* gene rearrangements by FISH and RAD51 foci formation. It should be noted that PTEN loss and *ETS* rearrangements co-associate and are found in approximately 50% of prostate cancers. In addition that is emerging evidence to suggest that RAD51 foci formation is diminished in tumours with HR defects such as those with loss of PTEN and *ETS* rearrangements (15, 27, 41, 44).

See section 2.1 for a discussion of relevant biomarkers.

Biomarkers will be classified as either established markers of sensitivity to synthetic lethality with PARPi (e.g. *BRAC1* *-/-*, *BRAC2* *-/-*), or as exploratory biomarkers. Established biomarkers will have a guaranteed place in the biomarker classifier but exploratory biomarkers will have to be shown to have predictive ability from the trial data.

The correlation between biomarkers will first be examined using Spearman's rank correlation. If two biomarkers are highly correlated or known to be highly correlated from previous evidence one of the biomarkers will be dropped. The use of appropriate cut-points of continuous scores for individual biomarkers will be decided before examining their association with response.

For potential promotion to the classifier, a false discovery rate of 10% or less will be applied to all exploratory biomarkers, using the p-values from the univariate association with response (Fisher's exact test, $p < 0.10$ 2-sided). If evidence exists from other sources it may be incorporated into the assessment of specific biomarkers using meta-analysis to give an 'overall' p-value.

Secondly, identification of a multivariable predictive classifier will be undertaken using a significance level of 10% or less for the inclusion of the biomarker in the classifier (logistic regression). In the event of a tie, e.g. two or more classifiers with similar performance, a liberal approach will be adopted on the basis that it will be possible to exclude non-responsive biomarker groups at a later date. Standard prognostic factors may be included in the classifier if they are independent of the biomarkers.

The goal will be to develop a classifier which identifies a group with a response rate of 40% or more on the basis that the levels for inefficacy and efficacy are set at 30% and 50% respectively.

The biomarker defined subgroup satisfying the above criteria will be selected for validation in Part B. If olaparib successfully graduates from this, stage Part C will be undertaken. If convincing evidence arises from other translational studies of olaparib or other PARP inhibitors the IDMC will be asked to advise whether or not an analysis should take place.

Part B

The biomarker status of patients registered in Part B will be evaluated and only patients with the presence of the putative biomarker subgroup identified in Part A will be entered. Forty-four additional patients will be treated in this single stage, which assumes $H_0: p_0=0.3$; H_a ; $p_1=0.5$; $\alpha=0.05$ and $\beta=0.15$.

If **19 or more** of the **44 patients** respond (43%), then a proposal for a subsequent randomised controlled trial to investigate the predictive potential of the biomarker will be developed. If **18 or less** patients respond, the study will be terminated.

Further information regarding the sample size calculations of both parts A and B is shown in Appendix A. The detectable effects in the biomarker sensitive group assuming 80% power are presented on Appendix B.

14.2 Analysis populations

Analysis populations are defined as follows:

- **Intention to treat (ITT):** This population includes all patients registered into the study regardless of whether they are later found to be ineligible, a protocol violator, never treated or not evaluated. Patients for whom the primary endpoint cannot be evaluated will be treated as non-responders.
- **Evaluable-patient population:** This population contains all registered patients for whom the primary endpoint can be evaluated. A patient will be “evaluable” if **at least a bone scan or RECIST measurement is available. Where evaluability is difficult to define the final decision will rest with the IDMC.**
- **Per protocol (PP):** This population contains all registered patients who received at least 1 cycle of olaparib without major protocol violations.
- **Safety population:** This population includes all registered patients who received at least 1 dose of olaparib.

The analysis of the primary outcome will use the evaluable-patient population with sensitivity analyses in the ITT and per protocol populations. All other analyses will use the ITT population. The ITT and PP analyses will treat non-evaluable patients as non-responders. The safety population will be used to further characterise the safety profile of olaparib in advanced CRPC patients.

14.3 Primary Efficacy Endpoint

Response will be defined by:

- Objective response by modified RECIST (baseline lymph node size must be ≥ 2 cm to be considered a target lesion) (Appendix E) and / or
- Conversion of circulating tumour cell count (CTC) to $< 5/7.5$ ml blood nadir confirmed by at least two readings 4 weeks apart and / or
- PSA decline of $\geq 50\%$ (according to the PCWG2) (Appendix D)

Failure will be defined as:

- Progression by RECIST- increase in measurable lesion size(S) or new lesion AND/OR
- Progression by bone scan – see Appendix D

Response will be evaluated 6 months post registration. The last value of PSA, CTC count, CT scan and bone scan on or up to four weeks before the date of first study treatment will be used as the baseline value for this assessment. The response rate will be presented along with its exact two-sided 95% confidence interval.

14.4 Secondary Efficacy Endpoints

The following endpoints will be assessed 6 months post registration. However, decisions made within the trial to comply with the adaptive design will not necessarily require 6 months follow up on all patients, e.g. it may be possible to enter patients into the second stage of Part A when it is clear between 3 and 14 responses will occur in the first stage even though not all 30 patients have 6 months follow up.

PSA response and PSA progression are defined according to the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA value from cycle 1 day 1 (baseline). This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. The first PSA reading will be obtained at week 12.

Time-to-PSA Progression

For patients who have achieved a $\geq 50\%$ decrease from the cycle 1 day 1 (baseline), the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the **nadir** is documented. This must be confirmed by a second consecutive value obtained 4 or more weeks later. For patients without a PSA decrease of this magnitude or no decrease at all, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the **baseline** is documented. This must also be confirmed by a second consecutive value 4 or more weeks later. Time to PSA progression will be summarised using Kaplan-Meier methods.

Duration of PSA response

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the cycle 1 day 1 (baseline) value (must be confirmed by a second value) until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be assessed at the last PSA measurement. Duration of PSA response will be summarised by the median and presented along its 95% confidence interval.

PSA objective response rate (PSA-ORR)

The proportion of patients having achieved partial or complete response defined by PSA will be reported with the corresponding exact two-sided 95% confidence interval.

Pattern of PSA Responses

Waterfall plots will be presented (as per PCWG2 recommendations) that show the percentage of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy), as well as the maximum decline in PSA that occurs at any point after treatment. Waterfall plots provide a broader display of PSA changes than dichotomised responses.

CTC Response

The proportion of patients with a CTC conversion to $<5/7.5$ ml blood at nadir (confirmed by two readings at least 4 weeks apart) will be presented along an exact two-sided 95% confidence interval. Its association with PFS and OS will be examined via Cox regression models first univariately and subsequently in a multivariable model adjusting for potential confounders. Waterfall plots of CTC falls will also be presented that show the percentage change in CTC counts from baseline to 12 weeks as well as maximal CTC count declines that occur at any point after treatment.

The following endpoints will be evaluated using Kaplan and Meier methods:

Radiographic Progression Free Survival (rPFS)

Radiographic progression free survival (rPFS) will be defined by either RECIST progression and /or progression on bone scan (Appendix D and E). It will be measured from the date of registration to the first occurrence of radiographic progression or death from any cause. If no event exists, then rPFS will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Time to Radiographic Progression

Time to radiographic progression (progression defined by either RECIST progression and /or progression on bone scan) will be measured from the date of registration to the first occurrence of radiographic progression. Death from prostate cancer or any other cause without prior radiographic evidence of progression will not count as an event. If no event exists, then time to radiographic progression will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Progression Free Survival (PFS)

Progression free survival will be measured from the date of registration until radiographic progression, unequivocal clinical progression or death. If no event exists, then PFS will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Overall Survival (OS)

OS will be measured from the date of screening to the date of death (whatever the cause). Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow-up.

14.5 Tertiary/exploratory Endpoints

- **Pain palliation:**

Pain palliation will be assessed using the Brief Pain Inventory's (BPI Short Form) worst pain intensity score and average score. A composite of the four pain items (worst, least, average, right now) will be presented as supplemental information. Change in BPI score from baseline will be assessed at 6 months post registration. A reduction of two points in the worst pain score relates to an improvement of pain. The analgesic relief received will be described.

- **Safety Endpoint**

Safety analysis will be summarised using the safety population. Extent of exposure to study drug will be summarised and details will be provided. Treatment emergent adverse

events (AEs) are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose. Adverse events will be graded according to the NCI-CTCAE v4.02. Adverse events will be summarised by grade, according to the worst grade experienced. In addition, most frequently observed AEs will be summarised. In the summary of AE, an AE occurs more than once within a SOC and PT will be counted only once using the worst grade experienced. Serious AE and deaths observed within 30 days of the last dose of study treatment will be provided in a listing.

All adverse events resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of study drug will also be listed and tabulated by preferred term. Clinical laboratory test results will be collected pre-treatment and through 30 days post last dose of study treatment. All laboratory test results will be classified according to the NCI CTCAE v4.02 criteria. Standard reference ranges will be used for missing or discrepant normal ranges. Baseline laboratory test values are the results from the last blood samples drawn on or prior to the first day of study treatment. On-study laboratory test values are those results from blood samples drawn a day after the first study treatment up until 30 days after the last dose of study treatment.

- **Impact of treatment with olaparib on bone metastases imaging by DW-MRI.**

Diffusion-weighted MRI scan will be offered to patients recruited in part A and we expect approximately 50% acceptance rate. This analysis will be **purely exploratory** and we will examine whether response to olaparib expressed by changes in apparent diffusion coefficients produced by the DW-MRI scan correlate with 1) PSA decline, 2) CTC conversion and 3) radiological responses coming from conventional imaging. In 20 patients it is possible to detect a correlation coefficient of 0.6 which is equivalent to the parameter explaining 36% of the variation using a 2-sided 5% significance level.

14.6 Data Monitoring

An Independent Data Monitoring Committee will meet approximately every 6 months (or at intervals determined by them) to review accrual, safety and efficacy data. The replacement of patients who withdraw from the study or who are un-evaluative for reasons deemed not to be treatment related will be based on the advice of the committee. The committee will review the results of each interim analysis (progression from stage 1 to stage 2 and progression to part B) and will be asked to advise. For completeness a sensitivity analysis of the progression free rate calculated by the Kaplan Meier product limit method will also be presented in which withdrawals and deaths are censored. The summary statistic will be the progression free rate at 6 months together with its 95% one-sided confidence interval.

15 TRANSLATIONAL RESEARCH

Paraffin embedded tumour blocks or unstained sections from archival tumour tissue from the time of the original diagnosis or from a biopsy / resection of metastatic disease will be required from all subjects who enrol on the study. Patients who do not have adequate

archival tumour tissue will be required to have tumour confirmed in a repeat tumour biopsy in order to be enrolled on the study. CTCs, urine, plasma samples and mandatory fresh tumour biopsies will be obtained at various time points during the study (Table 2 & 7). CTCs will be enumerated to evaluate conversion rates (CTC from ≥ 5 cells/7.5ml blood at baseline to < 5 cells/7.5mls) on this treatment. The tumour tissue will be assessed for multiple biomarkers including *PTEN* and *ERG* expression, *PTEN* deletions, *TMPRSS2-ETS* gene rearrangements using multicolour FISH studies, markers of DNA damage and HR repair such as γ H2AX and RAD51 focus formation, markers of tumour cell proliferation and cell cycle phase. Blood samples for plasma-based biomarker will be utilised for several studies including obtaining normal germline DNA and circulating tumour DNA for mutational analysis (e.g. *BRCA1*, *BRCA2*, *CHEK2*, etc.), quantitative real time polymerase chain reaction for *ERG* detection, proteomics, metabolomics, RNA and microRNA (miRNA) studies. Urine samples will be utilised to evaluate metabolomics, RNA and urine telopeptides profiles. Additional putative predictive biomarkers involved in the HR DNA repair pathway and sensitivity to PARP inhibition may be evaluated to facilitate the characterisation optimal determinants of response and resistance to olaparib treatment. Some of these additional markers/studies may come from other translational studies.

All the tumour tissue, CTC, plasma and urine samples will be sent to the Institute of Cancer Research Biomarker Group for processing and analysis. Some of these samples may be labelled with the patients' initials, hospital pathology number and trial number when they are sent to the research laboratory. When they arrive at the laboratory each sample will be coded with a unique anonymised number and any personal details removed. The number generated is linked to the patient trial ID held at the ICR CTSU. This coding system will maintain patient confidentiality whilst allowing biological details to be compared to treatment findings.

Samples will be stored in a secure area in the Cancer Biomarkers Laboratory at the Institute of Cancer Research. Samples will only be accessible by accredited staff involved in the processing and analysis of the samples. Some of the tumour/plasma samples collected may need to be sent to another site for processing and analysis. This will only occur following an established agreement being set up and assurance that patient confidentiality is maintained. **Instructions for the sample requirements, collection, handling, labelling, shipment and storage will be provided in a reference Laboratory Manual for Investigators.**

In some cases the archival tumour blocks will be returned to the local laboratories after the study is complete, depending on local practice. Patients participating on this study will be asked to give permission for possible future research into prostate cancer using these samples. The confidential nature of the tissue and associated data will be fully protected, and any other research using your tissue will first be reviewed and approved by an ethics committee.

These tumour and plasma samples may be used for, but not restricted to, the elucidation of mechanism of response, understanding the mode of action of olaparib and improving the understanding of disease progression.

Archival Tumour Blocks and Fresh Biopsies

An adequately sized (minimum of 2 mm x 2 mm) archival tumour tissue paraffin block from resection or a core biopsy from the time of the original diagnosis or from a biopsy / resection of metastatic disease at anytime prior to study entry is required. Alternatively, unstained slides prepared from the block can be provided. Mandatory fresh biopsies should be obtained at baseline (during the screening period; anytime between Day-28 to Day1), post commencement of treatment (during Cycle 1; anytime between Day 8 and Day 28) and at study discontinuation. The third biopsy is optional and will be obtained at any point between the patient coming off study treatment to the end of study visit.

The fresh tumour biopsy may be obtained from either the prostate or a metastatic site that is safe and amendable to a biopsy. Tumour biopsies may be obtained from the prostate itself (if it has not been surgically resected and has not been treated with radiotherapy) via an ultrasound-guided transrectal biopsy. Local recommendations for the procedure will be followed. Alternative sites where a biopsy can be obtained include lymph nodes, bone or liver where there is evidence of cancer on imaging. Patients who do not have evidence of visceral disease but do have evidence of bone metastasis on the bone scan may undergo a bone biopsy and aspirate from the ischium. Biopsies will be performed under radiological guidance as a day case whenever feasible. Ideally, the pre- and post-treatment biopsies will be from the same site. Collecting, handling procedures, shipping requirements and storage conditions will be provided in the TOPARP Laboratory Manual.

Circulating Tumour Cell (CTC) Assessments

A total of 18 blood samples will be drawn over 9 study visits for each patient enrolled during the first 12 months of treatment. Baseline samples will be collected at screening and one Cycle 1 Day 1 and subsequently CTC blood samples will be collected at Cycle 1 day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, every third cycle thereafter and at time of discontinuation of study treatment. CTCs will be enumerated using Veridex CellSearch™ platform. Patients being enrolled at the Royal Marsden NHS Foundation Trusts will have an additional 2 samples collected; an additional sample at screening and at Cycle 1 Day 1 (Table 7). CTC samples in all patients will be used to enumerate CTC counts and evaluate the molecular profile of tumour cells. Samples will be collected and shipped according to specified detail in the TOPARP Laboratory Manual. Amongst the molecular markers that will be studied include:

Immunofluorescence: PTEN, ERG, RAD51, γ H2AX and markers of tumour cell proliferation and cell cycle phase.

FISH: Including *PTEN*, *TMPSS2/ERG*

Plasma and Urine-Based Biomarkers

Plasma and urine samples for different analyses will be collected at multiple time points during the study (refer to Table 7 for details on the specific samples). These samples will be utilised for the purpose of analysing circulating plasma biomarkers including circulating tumour DNA and RNA for mutational analyses, quantitative real time polymerase chain

reaction of ERG detection, plasma proteomic signature, plasma and urine metabolomic studies and microRNA (mirRNA) profiles. Proteomic, metabolomic and miRNA profiling may generate signatures that can be used as predictive, prognostic and pharmacodynamic biomarkers that may also be correlated with other study endpoints. Samples will be collected and processed according to specified detail in the TOPARP Laboratory Manual.

LC-MS metabolomics: Blood and urine samples will be obtained at screening, on Cycle 1 Day 1 (pre-dose and 2hour post-dose), Cycle 1 Day 8 (pre-dose and 1hour post-dose), and Day 1 of subsequent cycles 2, 3 and 6 (-5 min pre-dose and 2hour post-dose).

PAXgene miRNAs Analyses: Whole blood samples will be collected at screening, Cycle 1 Day 1, and Day 1 of subsequent cycles 3, 5 and at either the treatment termination visit or the end of study.

Proteomic profiling: Plasma samples will be obtained at screening, Cycle 1 Day 1 (pre-dose) and at the end of the study or at the treatment termination visit.

Circulating Plasma DNA and RNA: Plasma samples will be collected at screening, Cycle1 Day 1, Cycle 1 Day 8 and on Day 1 of Cycles 2, 3, 5 and at the end of study or treatment termination visit.

Urine Markers of Bone Turnover (telopeptides): 24 hour urine samples will be collected at screening, Cycle 1 Day 1 and Cycle 3 Day1, Cycle 6 Day 1 and at the end of study or treatment termination visit.

Diffusion-weighted MRI

Diffusion-weighted MRI (DW-MRI) will be performed on an optional basis in a subset of patients. DW-MRI provides better visualisation of tumour cellularity and the results of DW-MRI will be correlated with bone scan results, PSA, CTC counts and patient outcome.

The intent of the biomarker / translational research embedded in this protocol is outlined below:

- To characterise the molecular profile of prostate cancer and sub-divide this heterogeneous disease.
- To develop predictive biomarkers of olaparib sensitivity which may be utilised to optimise patient selection for future studies
- To correlate the molecular profile of prostate cancer (in particular but not exclusively *PTEN*, *ERG* status by both IHC and FISH analysis) with clinical outcome
- To determine target modulation from olaparib treatment by the generation of γ H2AX foci formation, a marker of DNA damage in fresh biopsies and CTCs
- To evaluate the utility of early changes to CTC counts as a surrogate of clinical benefit to PARP inhibitors in CRPC
- To correlate CTC changes with PSA and radiological responses to olaparib treatment in CRPC

TIME POINTS	BLOOD BASED BIOMARKERS						URINE BIOMARKERS
	CTC	Plasma DNA & RNA Analyses	PAXgene miRNA	Plasma Proteomic Profile	Plasma Metabonomic Profiling	Urine Metabonomic profiling	Bone markers of turnover
Screening*	2x10mls	3x10mls	1x2.5mls	1x10mls	2x6mls	2 samples	24 urine collection
Cycle 1 day 1*	2x10mls	3x10mls	1x2.5mls	1x10mls	2x6mls	2 samples	24 urine collection
Cycle 1 day 8	2x10mls				2x6mls	2 samples	
Cycle 1 day 15	2x10mls						
Cycle 2 day1	2x10mls	3x10mls			2x 6mls	2 samples	
Cycle 3 day1	2x10mls	3x10mls	1x2.5mls		2x6mls	2 samples	24 urine collection
Cycle 4day1	2x10mls						
Cycle 5 day1		3x10mls	1x2.5mls				
Cycle 6 day1					2x6mls	2 samples	24 urine collection
Cycle 7day1 & every 3rd cycle thereafter	2x10mls						
End of Study Visit	2x10mls	3x10mls	1x2.5mls	1x10mls	2x6mls	1 sample	24 urine collection

Table 7: Summary of the blood and urine-based biomarker samples for the translational research

* Patients recruited at the Royal Marsden NHS Foundation Trusts will have an additional (3x10mls) CTC sample collected at screening and Cycle1Day1.

For total volumes of safety and research bloods refer to Appendix J.

16 TRIAL MANAGEMENT

The trial will be coordinated by ICR-CTSU in accordance with their quality management system.

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, Co-investigators and identified collaborators, the Trial Statistician and the Trial Managers. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of centres and professional groups. Notwithstanding the legal obligations of the Co-Sponsors and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. Where possible, membership will

include a lay/consumer representative. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and will include an independent Chairman (not involved directly in the trial other than as a member of the TSC) and not less than two other independent members. It is the role of the TSC to monitor progress of the trial and to ensure there is adherence to the protocol and the principles of Good Clinical Practice. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16.3 Independent Data Monitoring Committee (IDMC)

An IDMC will be instigated to monitor the progress of the trial. Membership of the IDMC will be proposed by the TMG and approved by the TSC. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU. The IDMC should meet in confidence at regular intervals, and at least every 6 months. A report of the findings and recommendations will be produced following each meeting. This report will be submitted to the TMG and TSC, and if required, the main REC and the MHRA.

The IDMC reserve the right to release any data on outcome or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

17 RESEARCH GOVERNANCE

This Clinical Trial will be conducted in accordance with the ethical principles laid down by the Declaration of Helsinki, 1964 and as amended in 1996 and the principles of Good Clinical Practice.

17.1 Sponsor Responsibilities

The Co-sponsors are The Institute of Cancer Research (ICR) and The Royal Marsden NHS Foundation Trust (RMH). Sponsorship activities and delegated responsibilities are shared between ICR and RMH, in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. Responsibilities of the Co-sponsors are set out in an agreement letter between ICR and RMH.

17.2 Principal Investigator Responsibilities

Responsibilities of each Principal Investigator and participating centre will be detailed in a contract with the Co-sponsors.

Principal Investigator responsibilities include putting and keeping in place arrangements to run the trial at their site according to the trial protocol and applicable guidance notes, The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. The above responsibilities include, but are not limited to, the following:

- Putting and keeping in place arrangements to adhere the principles of GCP
- Keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving and destruction of documentation once the trial has ended as required by regulation 31 of the principal Regulations of the Medicines for Human Use (Clinical Trials) Regulations 2004 implementing the commission directive 2005/28EC
- Ensuring investigational medicinal products (IMPs) are made available to subjects free of charge
- Taking appropriate urgent safety measures and
- Ensuring recording and prompt reporting of SAEs/SARs to ICR-CTSU

ICR is responsible for co-ordinating any required legal agreements and investigator statements.

The delegation of sponsorship responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership and as such it is necessary to share pertinent information between ICR and RMH/Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

17.3 AstraZeneca Responsibilities

AstraZeneca are responsible on behalf of the co-sponsors for the manufacture, packing, labelling and distributing of study drug and matching placebo to site in accordance with Good Manufacturing Practice and all applicable local legislation. Some of these responsibilities have been delegated by AstraZeneca to Fisher Clinical Services. Responsibilities are defined in an agreement between AstraZeneca and the co-sponsors, and AstraZeneca and Fisher Clinical Services.

18 TRIAL ADMINISTRATION & LOGISTICS

18.1 Protocol Compliance

The TOPARP Trial is being conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the EU Clinical Trials Directive. Before activating the trial, participating centres are required to sign an agreement accepting responsibility for all trial activity which takes place within their centre.

Sites may commence recruitment once centre agreements have been signed by both parties, trial documentation is in place and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

18.2 Data Acquisition

ICR-CTSU is responsible for the data management and statistical analysis of trial data. ICR-CTSU will supply CRFs to participating sites for the collection of trial specific data. The Trial Management Group reserves the right to amend or add to the CRF as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres in accordance with the guidelines provided by ICR-CTSU.

The clinical data should be recorded on the TOPARP case report forms (CRFs) and the relevant pages forwarded to ICR-CTSU in a timely manner.

By participating in the TOPARP trial, the Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure that:

- Sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs;
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- All staff at their centre who are involved with the trial will meet the requirements of the EU Directive;
- Original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent;
- All essential documents must be retained for five years after the Trial ends to comply with current legislation.
- Staff will comply with the protocol and Trial Guidance Notes for the TOPARP trial.

On receipt at ICR-CTSUS, CRFs will be recorded as received and any missing forms will be reported to the originating site. Illegible forms may be returned to site for clarification.

18.3 Central Data Monitoring

ICR-CTSUS will review incoming CRFs for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be sent to the relevant centre for resolution. Following initial review, the CRF data items will be entered into the clinical study database held at ICR-CTSUS.

Data will be further reviewed for data anomalies / missing data, by central statistical monitoring. Any systematic inconsistencies identified may trigger monitoring visits to centres.

18.4 On-Site Monitoring

Site monitoring will be conducted at participating centres at least once during the course of the trial. Additional on-site monitoring may be triggered by routine central statistical monitoring or identification of a new risk to the trial.

If a monitoring visit is required, ICR-CTSUS will contact the centre to discuss dates of proposed visit. Once a date has been confirmed, the centre should ensure that the relevant patient notes are available for monitoring.

If any problems are detected in the course of the monitoring visit, ICR-CTSUS will work with the Principal Investigator to resolve issues and, if necessary, to determine the centre's future participation in the study.

ICR-CTSUS staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the site agreement and trial protocol to ensure the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996.

18.5 End of trial

The end of trial for MHRA and MREC purposes is the date of last data capture

18.6 Archiving

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. Essential documents will be maintained at ICR-CTSUS in a way that will facilitate the management of the trial, audit and inspection. They should be retained for a sufficient period (at least 15

years) for possible audit. Documents should be securely stored and access restricted to authorised personnel.

19 PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

The trial will have received ethical, regulatory and institution specific approvals prior to recruitment of any patients into the study. Before entering patients, the Principal Investigator at each site is responsible for gaining Site Specific Assessment and Research and Development approval of this protocol.

Patients should be asked to sign the trial consent forms after receiving both verbal and written information about the trial. All consent forms must be countersigned by the Principal Investigator or a designated individual. A record listing the designated individuals and the circumstances under which they may countersign consent forms must be clearly documented at the research site as part of the Delegation of Responsibilities Log. This log, together with original copies of all signed patient consent forms, must be available for inspection.

The TOPARP patient information sheets should be provided in addition to any standard patient information sheets that are provided by the centre and used in routine practice.

19.1 Patient Confidentiality

Patients will be asked to consent to their full name being collected at registration in addition to their date of birth, hospital number, postcode and NHS number (CHI in Scotland) to allow tracing through national records to assist with long term follow up and to allow linkage with routinely collected NHS data. The personal data recorded on all documents will be regarded as confidential, and any information which would allow individual patients to be identified will not be released into the public domain.

Each investigator should keep a separate log of all patients' Trial IDs, names, addresses and hospital numbers. The investigator must maintain trial documents, which are to be held at the participating centres (e.g. patients' written consent forms), in strict confidence. The investigator must ensure the patients' confidentiality is maintained.

ICR-CTSU will maintain the confidentiality of all patients and will not reproduce or disclose any information by which patients could be identified. Representatives of ICR-CTSU and the regulatory authorities will be required to have access to patients notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries it is also necessary to have access to the complete study records provided that patient confidentiality is protected.

19.2 Data Protection

ICR-CTSU will comply with all applicable data protection laws. Any requests from patients for access to data about them held at ICR-CTSU should be directed to the Trial Manager in the first instance who will refer the request to the Data Protection Officer at The Institute of Cancer Research.

19.3 Liability

The Co-Sponsors have taken out an insurance policy to cover their study responsibilities, and certification of this will be provided to the regulatory authorities as required. ICR-CTSU will need to be satisfied that all participating sites have appropriate indemnity arrangements in place.

20 FINANCIAL MATTERS

The trial is investigator designed and led and has been approved by Clinical Trials Advisory & Awards Committee (CTAAC) of Cancer Research UK, and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

ICR has received funding from Cancer Research UK and AstraZeneca (via the AstraZeneca/NCRN collaboration) for the central coordination of the trial. AstraZeneca are also providing olaparib for the purposes of this trial free of charge.

In the UK, the trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research (NIHR) portfolio by virtue of its approval by CTAAC. Therefore, National Cancer Research Network (NCRN) resources should be made available for the TOPARP trial to cover UK specific research costs.

21 PUBLICATION POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group led by the chief investigator, appointed from amongst the Trial Management Group, and participating clinicians. All participating centres and clinicians will be acknowledged in this publication together with the dedicated staff from the ICR-CTSU. All presentations and publications relating to the trial must be authorised by the Trial Management Group, on whose behalf publications should usually be made. Authorship of any secondary publications e.g. relating to the various biological studies will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present

or attempt to publish data relating to the TOPARP trial without prior permission from the Trial Management Group.

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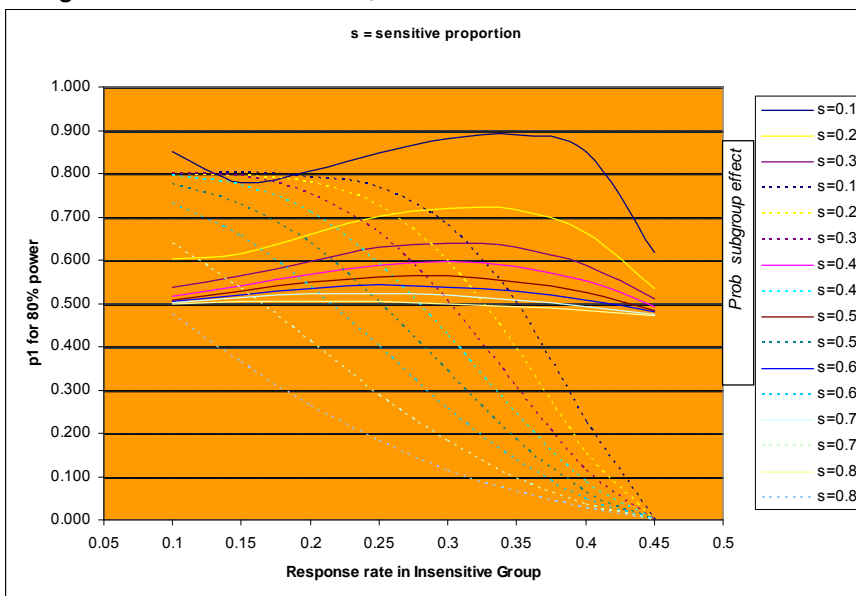
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23 APPENDICES

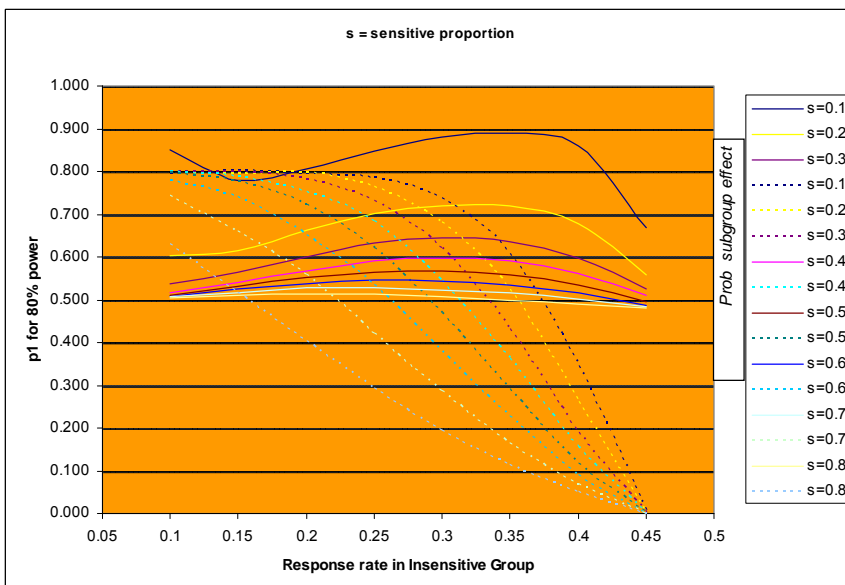
23.1 Appendix A: Detectable Effects

It is possible to calculate detectable effects in the sensitive group (80% power, y-axis) based on the proportion of sensitive patients (individual lines) and the response rate (x-axis) in the insensitive subgroup. Also shown is the probability a subgroup effect is detected (dashed lines), with 80% power this probability cannot exceed 80%. The fall in the probability of detecting a subgroup effect with increasing response rate in insensitive patients is therefore balanced by an increase in the probability of detecting an overall effect. Thus, in the extreme, if the response rate in insensitive patients is 45% and the response rate in sensitive patients is about 50% a conclusion of overall efficacy will be reached with 80% power, for subgroups of size 30% or more.

Using cut offs for Part A of $a_0=15/30$, $a_1=23/45$, as intended.



Using cut offs for Part A of $a_0=18/30$, $a_1=27/45$ the probability of detecting a subgroup effect if the sensitive group is large (>50%) can be improved.



23.2 Appendix B: Sample Size Calculations

TOPARP sample size calculations, **Part A** : alpha 2.2%, Power 90%

Ho : Null Hypothesis Response rate (p0) is 5%

Probability reject **0.97818** *alpha* 2.2%

Reject first stage **0.81218** (Probability of early termination, sum of values in light blue)

Reject second stage **0.166** (sum of values in dark blue)

sum 0.97818

N	po	N second stage										
First		0	1	2	3	4	5	6	7	8	15
0	0.214639	0.46329	0.3657562	0.13475	0.03073	0.00485	0.00056	4.9E-05	3.3E-06	1.8E-07	3.1E-20
1	0.338903	0.059	0.046	0.017	0.004	0.001	0	0	0	0		0
2	0.258637	0.021	0.017	0.006	0.001	0	0	0	0	0		0
3	0.12705	0.006	0.005	0.002	0	0	0	0	0	0		0
4	0.045136	0.001	0.001	0	0	0	0	0	0	0		0
5	0.012353	0	0	0	0	0	0	0	0	0		0
6	0.002709	0	0	0	0	0	0	0	0	0		0
7	0.000489	0	0	0	0	0	0	0	0	0		0
8	7.4E-05	0	0	0	0	0	0	0	0	0		0
9	9.52E-06	0	0	0	0	0	0	0	0	0		0
10	1.05E-06	0	0	0	0	0	0	0	0	0		0
11	1.01E-07	0	0	0	0	0	0	0	0	0		0
12	8.39E-09	0	0	0	0	0	0	0	0	0		0
13	6.11E-10	0	0	0	0	0	0	0	0	0		0
14	3.91E-11	0	0	0	0	0	0	0	0	0		0
15	2.19E-12											
16	1.08E-13											
17	4.69E-15											
18	1.78E-16											
.....												
26	3.33E-30											
27	2.59E-32											
28	1.46E-34											
29	5.31E-37											
30	9.31E-40											

Stage I 2.31E-12
probability of incorrect stopping

H1 : Null Hypothesis Response rate (p1) is 20%

Probability reject **0.10318** *Power* 89.7%

Reject first stage **0.04418** (Probability of early termination, sum of values in light blue)

Reject second stage **0.059** (sum of values in dark blue)

N	po	N second stage										
First		0	1	2	3	4	5	6	7	8	15
0	0.001238	0.03518	0.1319414	0.2309	0.25014	0.1876	0.10318	0.04299	0.01382	0.00345	3.3E-11
1	0.009285	0.003	0.01	0.018	0.02	0.015	0.008	0.003	0.001	0		0
2	0.033656	0.005	0.017	0.031	0.033	0.025	0.014	0.006	0.002	0		0
3	0.078532	0.006	0.023	0.04	0.043	0.032	0.018	0.007	0.002	0.001		0
4	0.132522	0.006	0.024	0.041	0.045	0.034	0.019	0.008	0.002	0.001		0
5	0.172279	0.005	0.02	0.036	0.038	0.029	0.016	0.007	0.002	0.001		0
6	0.179457	0.004	0.015	0.026	0.028	0.021	0.011	0.005	0.002	0		0
7	0.153821	0.002	0.009	0.016	0.017	0.013	0.007	0.003	0.001	0		0
8	0.110559	0.001	0.005	0.008	0.009	0.007	0.004	0.002	0	0		0
9	0.067564	0.001	0.002	0.004	0.004	0.003	0.002	0.001	0	0		0
10	0.035471	0	0.001	0.001	0.002	0.001	0.001	0	0	0		0
11	0.016123	0	0	0.001	0.001	0	0	0	0	0		0
12	0.006382	0	0	0	0	0	0	0	0	0		0
13	0.002209	0	0	0	0	0	0	0	0	0		0
14	0.000671	0	0	0	0	0	0	0	0	0		0
15	0.000179											
16	4.19E-05											
17	8.63E-06											
18	1.56E-06											
.....												
26	7.53E-15											
27	2.79E-16											
28	7.47E-18											
29	1.29E-19											
30	1.07E-21											

Stage I 0.000231
probability of incorrect stopping

TOPARP sample size calculations, **Part A**, rule to be applied if no subgroup is found:

Ho : Null Hypothesis Response rate (p0) is 30%

<u>N</u>	<u>p0</u> 0.3	Reject first stage	0.94505 (sum of values in light blue)	alpha	5.5%
0	1.07E-07	16	0.0896266	32	1.3E-08
1	2.06E-06	17	0.0655253	33	2.2E-09
2	1.95E-05	18	0.0436835	34	3.3E-10
3	0.00012	19	0.0266043	35	4.5E-11
4	0.000538	20	0.0148224	36	5.4E-12
5	0.00189	21	0.0075624	37	5.6E-13
6	0.005401	22	0.0035357	38	5E-14
7	0.012895	23	0.0015153	39	3.9E-15
8	0.026251	24	0.0005953	40	2.5E-16
9	0.046252	25	0.0002143	41	1.3E-17
10	0.071361	26	7.065E-05	42	5.3E-19
11	0.09731	27	2.131E-05	43	1.6E-20
12	0.118162	28	5.87E-06	44	3.1E-22
13	0.12855	29	1.475E-06	45	3E-24
14	0.125927	30	3.371E-07		
15	0.111535	31	6.991E-08		

Ha : Alternate Hypothesis Response rate (p1) is 50%

<u>N</u>	<u>p1</u> 0.5	Reject first stage	0.11635	Power	88.4%
0	2.84E-14	16	0.0183782	32	0.00207
1	1.28E-12	17	0.0313511	33	0.00082
2	2.81E-11	18	0.0487684	34	0.00029
3	4.03E-10	19	0.0693024	35	9.1E-05
4	4.23E-09	20	0.0900931	36	2.5E-05
5	3.47E-08	21	0.1072537	37	6.1E-06
6	2.31E-07	22	0.1170041	38	1.3E-06
7	1.29E-06	23	0.1170041	39	2.3E-07
8	6.13E-06	24	0.1072537	40	3.5E-08
9	2.52E-05	25	0.0900931	41	4.2E-09
10	9.07E-05	26	0.0693024	42	4E-10
11	0.000288	27	0.0487684	43	2.8E-11
12	0.000817	28	0.0313511	44	1.3E-12
13	0.002075	29	0.0183782		
14	0.004743	30	0.0098017		
15	0.009802	31	0.0047428		

TOPARP sample size calculations, **Part B** :

Ho : Null Hypothesis Response rate (p0) is 30%

<u>N</u>	<u>p0</u> 0.3	Reject first stage	0.95628 (sum of values in light blue)	alpha	5%
0	1.53E-07	16	0.0825133	32	5.4E-09
1	2.88E-06	17	0.0582447	33	8.4E-10
2	2.66E-05	18	0.037443	34	1.2E-10
3	0.000159	19	0.0219591	35	1.4E-11
4	0.0007	20	0.0117638	36	1.5E-12
5	0.0024	21	0.0057619	37	1.4E-13
6	0.006687	22	0.0025816	38	1.1E-14
7	0.015556	23	0.0010583	39	7.4E-16
8	0.030835	24	0.0003969	40	4E-17
9	0.05286	25	0.0001361	41	1.7E-18
10	0.07929	26	4.261E-05	42	5.1E-20
11	0.105033	27	1.218E-05	43	1E-21
12	0.123789	28	3.168E-06	44	9.8E-24
13	0.130591	29	7.491E-07		
14	0.123928	30	1.605E-07		
15	0.106224	31	3.107E-08		

Ha : Alternate Hypothesis Response rate (p1) is 50%

<u>N</u>	<u>p1</u> 0.5	Reject first stage	0.14561	Power	85%
0	5.68E-14	16	0.0236875	32	0.0012
1	2.5E-12	17	0.0390147	33	0.00044
2	5.38E-11	18	0.058522	34	0.00014
3	7.53E-10	19	0.0800828	35	4E-05
4	7.72E-09	20	0.1001035	36	1E-05
5	6.17E-08	21	0.114404	37	2.2E-06
6	4.01E-07	22	0.1196042	38	4E-07
7	2.18E-06	23	0.114404	39	6.2E-08
8	1.01E-05	24	0.1001035	40	7.7E-09
9	4.03E-05	25	0.0800828	41	7.5E-10
10	0.000141	26	0.058522	42	5.4E-11
11	0.000436	27	0.0390147	43	2.5E-12
12	0.001199	28	0.0236875	44	5.7E-14
13	0.002951	29	0.013069		
14	0.006534	30	0.0065345		
15	0.013069	31	0.0029511		

23.3 Appendix C: Evidence of PD to Determine Trial Entry Eligibility

Patients being considered for trial entry should have evidence of disease progression by either PSA, modified RECIST or bone scan to be eligible.

PSA: PSA evidence of disease progression based on the prostate cancer working group (PCWG) 2 criteria consist of a minimum PSA level 2.0 ng/ml that has risen on at least 2 successive occasions, at least 1 weeks apart. The reference value # 1 is the last value before the rise in PSA was observed. If the confirmatory PSA value (Figure 5, # 3A) is greater than the screening value then progression by PSA is met and the patient is eligible for trial enrolment on the basis of PSA alone. If the confirmatory PSA (Figure 5, #3B) value is less than the screening PSA (Figure 5, #2) value, then an additional test for rising PSA (#4) will be required to document progression before the patient can be enrolled.

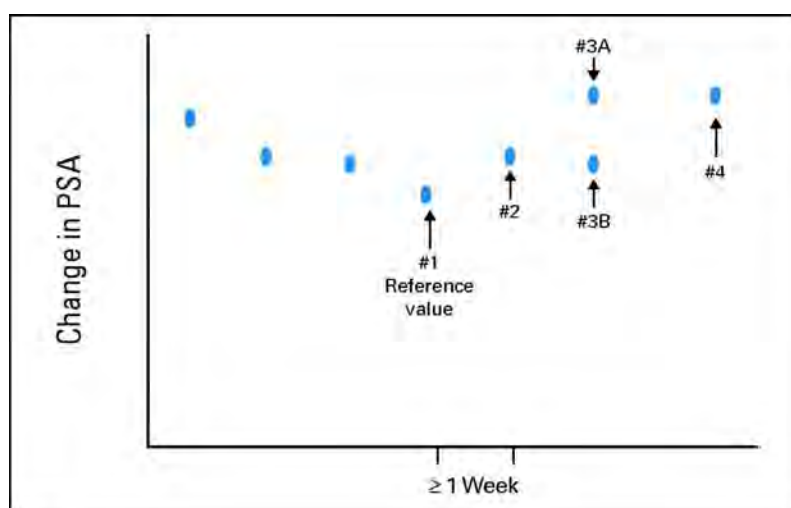


Figure 5: Eligibility Based on PSA

Target lesion/measurable disease: Patients are not required to have evidence of disease progression by measurable disease if they meet the criteria for disease progression on the basis of PSA or bone scan. Evidence of nodal or visceral disease RECIST progression however is sufficient for trial entry independent of PSA readings. Because lymph nodes may be enlarged due to benign pathology, only lymph nodes that are ≥ 2 cm should be used for disease evaluation.

Bone scan: Evidence of disease progression based on bone scan appearance is sufficient for trial entry independent of PSA readings. If the appearance of the bone scan is the only indicator of progression then there must be ≥ 2 new bone lesions compared with the prior bone scans. If there is ambiguity about the appearance of the bony lesions such as traumatic in nature or secondary to a flare reaction then it is recommended that an alternative imaging modality such as MRI or fine-cut CT be used to evaluate these lesions further.

23.4 Appendix D: Outcome Measures of Response / Progression Post Study Treatment

Procedures for Assessing PSA Response / Progression Post Study Treatment

PSA measurements will be done every 12 weeks on day1 of cycle 4,7,10 and every 3rd cycle thereafter. Increases and decreases will be tracked in order to assess disease response. The PSA readings on its own will not be used to define progression in this protocol. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG 2:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA from cycle1day1 (baseline) PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. The first PSA reading will be obtained at week 12.

Duration of PSA Response:

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the Cycle 1 Day 1 (baseline) value that has been confirmed by a second value until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be assessed at the last PSA measurement.

Time to PSA Progression:

For patients who have achieved a $\geq 50\%$ decrease from the Cycle 1 Day 1 (baseline), the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 4 or more weeks later. For patients without a PSA decrease of this magnitude or without a decrease, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented, which is confirmed by a second consecutive value 4 or more weeks later.

Procedures for Assessing Radiological Responses / Progression Post Study Treatment

Categorisation of response in this study will be based on modified RECIST 1.1 for soft tissue disease and appearance of bone scan for bone metastasis.

Bone metastasis evaluation:

The first bone scan should not be performed before 12 weeks post commencement of treatment unless clinically indicated as there may be evidence of a flare response early on which may confuse the response evaluation. A patient will be considered to have progressed on bone scan if the following criteria are met:

- If the first bone scan with 2 new lesions is observed ≤ 13 weeks from the point of Cycle 1 Day 1 and is confirmed by a follow up scan ≥ 6 weeks later showing 2 additional new lesions (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan).
- The first bone scan with ≥ 2 new lesions compared with baseline is observed > 13 weeks from Cycle 1 Day 1 and the new lesions are verified on the next bone scan ≥ 6 weeks later (i.e. a total of ≥ 2 new lesions compared with baseline). If the second scan confirms progression the data of the progression is the date of the first bone scan rather than the second confirmatory scan.

Measurable Disease Evaluation:

Changes in nodal and visceral disease should be recorded using the modified RECIST criteria defined in Appendix E.

Table 8: Radiological Criteria for Ascribing Disease Progression

Evidence of Progression	Confirmation	Action
Bone Disease Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment ≤ 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show an additional 2 new lesions compared to the first post treatment scan (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment > 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should confirm the presence of the 2 new lesions compared the baseline scan. (i.e. a total of ≥ 2 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Soft Tissue Disease as defined by RECIST on CT/MRI	Progression at any scheduled reassessment ≥ 12 weeks does not need to be confirmed.	Investigators are highly encouraged to maintain the patient's treatment with study medication unless radiological progression is observed.

Progression Free Survival (PFS)

In this protocol death, radiographic and unequivocal clinical progression comprise the PFS events. PFS is defined from the time of study entry to confirmed disease progression based on either:

- Radiological progression as documented on bone scans and / or measurable disease on CT scans

OR

- Unequivocal clinical progression

OR

- Death

The analysis of PFS is based on the time of the first progression observed. Where possible all disease assessment (Bone scan, CT, PSA) should be collected at the same time points.

23.5 Appendix E: Modified RECIST

The primary efficacy objective to this trial is based on tumour assessment. For the purpose of this study, definitions of soft tissue tumour assessments will be based on a Modified Response Evaluation Criteria in Solid Tumours 1.1 (RECIST1.1). Pertinent points are summarised below.

Evaluation of measurable and non-measurable lesions

1. **Measurable lesions** – lesions that can be accurately measured in at least one dimension with the longest diameter \geq 20 mm using conventional techniques or \geq 10 mm, with a spiral CT scan.
2. **Non-measurable lesions** – all other lesions, including small lesions (longest diameter \leq 10 mm, with a spiral CT scan), i.e., blastic bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
3. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, should not be included in assessment of response, but should be assessed for progression.
4. For this study, bone lesions are not considered “non-measurable” lesions for RECIST. Bone lesions will be assessed by bone scan only.
5. All measurements should be taken and recorded in metric notation, using a ruler or calipers. Preferably, all screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.
6. The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up.
7. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion is recommended.

Methods of measurement:

1. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.

2. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung, however CT scans are preferable.
3. Ultrasound (US), endoscopy and laparoscopy should not be used to measure tumour lesions. It is however a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound may also be used to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
4. Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions).

Baseline documentation of target and non-target lesions

1. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline and at the time points specified in the protocol.
2. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements.
3. A sum of the longest diameters (LD) for all target lesions will be calculated and reported as the baseline sum of LD. The baseline sum LD will be used as reference by which to characterise the objective tumour response.
4. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions will also be monitored throughout the study, and an overall assessment of response will be made. Details of any new lesions will also be recorded. It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Table 9: Response Criteria

Response criteria	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD)	At least 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	Whether sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Table 10: Responses in patients with both target and non-target disease

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/nonPD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD= progressive disease, NE= inevaluable

Table 11: Responses in patients with only non-target disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/nonPD	No	Non-CR/nonPD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD= progressive disease, NE= inevaluable

Reproduced from: <http://www.recist.com/recist-comparative/01.html> and Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 12 weeks) that is defined in the study protocol.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

23.6 Appendix F: ECOG Performance Status

Table 12: ECOG Performance Status

ECOG Performance Status	Function
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead


23.7 Appendix G: National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.02)

V4.02 (CTCAE): publish date August 9, 2010:
ctep.cancer.gov/reporting/ctc.html

23.8 Appendix H: World Medical Association Declaration of Helsinki

<http://www.wma.net/e/policy/b3.html>

23.9 Appendix I: Brief Pain Inventory (Short Form)

 1903	Date: <input type="text"/> / <input type="text"/> / <input type="text"/> (month) (day) (year)	Study Name: _____ Protocol #: _____ PI: _____ Revision: 07/01/05
Subject's Initials: _____		
Study Subject #: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		

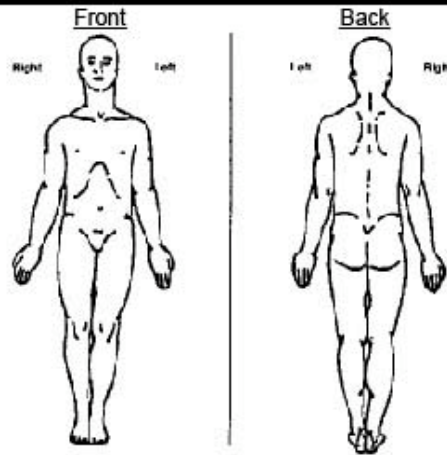
PLEASE USE BLACK INK PEN

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the **average**.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine



Date: / /
 (month) (day) (year)
 Subject's Initials : _____
 Study Subject #:

Study Name: _____
 Protocol #: _____
 PI: _____
 Revision: 07/01/05

PLEASE USE
BLACK INK PEN

7. What treatments or medications are you receiving for your pain?

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No Relief										Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with you:

A. General Activity
 0 1 2 3 4 5 6 7 8 9 10
 Does Not Interfere Completely Interferes

B. Mood
 0 1 2 3 4 5 6 7 8 9 10
 Does Not Interfere Completely Interferes

C. Walking ability
 0 1 2 3 4 5 6 7 8 9 10
 Does Not Interfere Completely Interferes

D. Normal Work (includes both work outside the home and housework)
 0 1 2 3 4 5 6 7 8 9 10
 Does Not Interfere Completely Interferes

E. Relations with other people
 0 1 2 3 4 5 6 7 8 9 10
 Does Not Interfere Completely Interferes

F. Sleep
 0 1 2 3 4 5 6 7 8 9 10
 Does Not Interfere Completely Interferes

G. Enjoyment of life
 0 1 2 3 4 5 6 7 8 9 10
 Does Not Interfere Completely Interferes

23.10 Appendix J: Total blood volumes drawn at each time point

Study time points	Months on study	Total volume of safety and research bloods per month
Screening	-1	92.5mls (102.5mls)*
Cycle 1 Day 1	1	156.5 mls (166.5mls)*
Cycle 1 Day 8		
Cycle 1 Day 15		
Cycle 2 Day 1	2	74mls
Cycle 3 Day 1	3	76.5mls
Cycle 4 Day 1	4	38mls
Cycle 5 Day 1	5	44.5mls
Cycle 6 Day 1	6	24mls
Cycle 7 Day 1	7	38mls
Cycle 8 Day 1	8	12mls
Cycle 9 Day 1	9	12mls
Cycle 10 Day 1	10	38mls
Cycle 11 Day 1	11	12mls
Cycle 12 Day 1	12	12mls
End of study		92.5mls
*Patients treated at the Royal Marsden Hospital will have an additional 10 ml sample of blood obtained at Screening and Cycle 1 Day 1		

TOPARP

Phase II Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer

Chief Investigator Prof. Johann de Bono

Co-Sponsors: The Royal Marsden Hospital NHS Foundation Trust /
The Institute of Cancer Research

Approval: Clinical Trials Advisory & Awards Committee
(CTAAC)

Funders: Cancer Research UK
AstraZeneca

Coordinating Trials Unit: Institute of Cancer Research Clinical Trials and
Statistics Unit (ICR-CTSU)

PROTOCOL Version 2.0 6th March 2012

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The TOPARP trial has been approved
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Health Research Clinical Research Network Trial Portfolio



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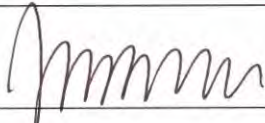
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This protocol describes the TOPARP trial and provides information about procedures for entering patients. The protocol should not be used as a guide for the treatment of other patients. Every care has been taken in the preparation of this protocol, however corrections or amendments may be necessary. These will be circulated to investigators in the trial. Centres entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version. Protocol amendments will be circulated to participating centres as they occur.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended. It will be conducted in compliance with the protocol, the Data Protection Act (Z6364106) and other regulatory requirements as appropriate.

Glossary of Abbreviations and Definitions of Terms

AD	Androgen deprivation
ADP	Adenosine diphosphate
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase (SGPT)
APTT	Activated partial thromboplastin time
AST	Aspartate Transaminase (SGOT)
AR	Androgen receptor
AZ	AstraZeneca
BID	Twice daily
BER	Base excision repair
BP	Blood Pressure
BUN	Blood urea nitrogen
°C	Degrees Celsius
FBC	Full Blood Count
cm	Centimetre
CR	Complete Response
CrCl	Creatinine clearance
CRF	Case Report Form
CRPC	Castration Resistant Prostate Cancer
CT	Computerised Tomography
CTC	Circulating Tumour Cell
CTCAE	Common Terminology Criteria for Adverse Events
D	Day (as in treatment day)
dL	Decilitres
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DRE	Digital rectal exam
DSB	Double Strand Breaks
DW-MRI	Diffusion-weighted MRI
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
FDA	Food and Drug Administration
FISH	Fluorescent in-situ hybridisation
FBC	Full Blood Count
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyltransferase
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
Ha	Alternative Hypothesis
H2AX	Histone H2AX
Ho	Null hypothesis
HR	Homologous Recombination
IB	Investigator Brochure
IC50	Dose for 50% inhibition
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IF	Immunofluorescence
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRB	Institutional Review Board
ITT	Intention To Treat
kg	Kilogram
LD	Longest Diameter
LDH	Lactic Dehydrogenase
LHRH	Luteinizing Hormone Releasing Hormone
mg	Milligram
MRI	Magnetic Resonance Imaging
miRNAs	MicroRNAs
NAD	Nicotine adenine dinucleotide
NCI	National Cancer Institute
NCICTC	National Cancer Institute Common Terminology Criteria
nM	Nanomolar
NRS	Numeric Rating Scale
ORR	Overall Response Rate
PARP	Poly (ADP-ribose) polymerase
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD	Pharmacodynamic
PFS	Progression Free Survival
PICF	Patient Informed Consent Form
PIN	Prostatic Intraepithelial Neoplasm
PK	Pharmacokinetic
PO	Per Oral (by mouth)
PR	Partial Response
PSA	Prostatic Specific Antigen
PCWG2	Prostate Cancer Working Group 2
PT	Preferred Term
PTEN	Phosphatase and Tensin Homologue
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SD	Stable disease
SUSAR	Serious unexpected suspected adverse (drug) reaction
SBP	Systolic blood pressure
SSB	Single Strand Break
SOC	System Organ Class
μM	Micromolar
ULN	Upper Limit of Normal
UA	Urinalysis
WBC	White Blood Cells

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1 TRIAL SUMMARY

PROTOCOL TITLE	Phase II Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer (TOPARP).
TARGET DISEASE	Castration resistant prostate cancer (CRPC)
STUDY OBJECTIVES	<ul style="list-style-type: none"> To evaluate the anti-tumour activity of olaparib in metastatic castration resistant prostate cancer To identify molecular signatures of tumour cells in responding and non-responding patients To clinically qualify putative predictive biomarkers of PARP inhibitor sensitivity
STUDY DESIGN	Open-label, single arm, two part adaptive design phase II trial.
TRIAL POPULATION	Patients with an advanced CRPC who have failed androgen deprivation and taxane-based treatment.
TREATMENT REGIMEN	Patients will receive single agent olaparib 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.
RECRUITMENT TARGET	Part A: between 30-45 patients Part B: 44 patients
PRIMARY ENDPOINT	Response will be defined on the basis of the following outcomes, if any of these occur patients will be considered to have responded: <ul style="list-style-type: none"> Objective response by modified RECIST PSA decline of $\geq 50\%$ according to the Prostate Cancer Working Group 2 (PCWG2) Conversion of circulating tumour cell count (CTC) from ≥ 5 cells/7.5 ml blood at baseline to < 5 cells/7.5 ml confirmed by at least two readings 4 weeks apart
SECONDARY ENDPOINTS	<ul style="list-style-type: none"> Radiological progression free survival Time to radiological progression Progression free survival Overall survival Time to PSA progression Proportion of patients with conversion of CTC count from $\geq 5/7.5$ml blood at baseline to $< 5/7.5$ ml blood nadir Duration of PSA response and objective response (PSA-ORR), if applicable Safety and tolerability of olaparib
EXPLORATORY ENDPOINTS	<ul style="list-style-type: none"> To evaluate the impact of treatment with olaparib on bone metastasis imaging by DW-MRI in selected patients and to correlate these results with PSA, CTC and radiological responses

	<p>by conventional imaging.</p> <ul style="list-style-type: none"> • To determine the proportion of patients achieving pain improvement with olaparib treatment.
<p>TRIAL OUTLINE</p>	<ul style="list-style-type: none"> • There will be screening period of up to 28 days prior to cycle 1 day 1. • Archival tissue is mandated for enrolment into the study. Patients who do not have a prior histological diagnosis or archival tissue available will be required to have a tumour biopsy. PART A of the study will be open to all comers. In PART B the tumour tissue of the patients being considered for enrolment will be analysed first to ensure the presence of the putative predictive biomarkers and only patients with the predictive biomarkers will be enrolled. • Patients will receive single agent 400mg of olaparib, twice daily, continuously on 28-day cycles. • During the study period, no other anticancer or hormonal treatment will be given although a LHRH analogue must be continued, unless the patient is surgically castrate. <p>Efficacy Assessments:</p> <ul style="list-style-type: none"> • Baseline CT scans, bone scan and DW-MRI (optional) will be performed as close as possible to cycle 1 day 1 of treatment. These scans will be repeated after every 3 cycles (12 weeks) or earlier if clinically indicated. • PSA will be assessed at baseline and every 12 weeks by PCWG2 criteria. In the absence of radiological disease progression patients should continue on study. <p>Safety Assessments:</p> <p>Safety parameters will be continuously assessed throughout the study prior to each cycle of treatment. Adverse events (AEs) and serious adverse events (SAEs) including laboratory tests will be graded and summarised according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events version 4.02 (CTCAE v4.02).</p> <p>Based on Phase I and Phase II studies, olaparib is generally well tolerated. Safety concerns are mainly related to the possibility of myelosuppression. Patients who experience a NCI-CTCAE grade 3-4 haematological or non-haematological toxicity that the investigator attributes to olaparib may have an interruption of olaparib treatment for up to 42 days until recovery of all toxicities to no more than NCI-CTCAE grade 1. Those patients on continuous treatment requiring a delay in dosing by >14 days will require a dose reduction to 300mg BID. If the adverse event recurs at the same severity, treatment can be interrupted again and on resolution to ≤ NCI-CTCAE grade 1 toxicity a further dose reduction to 200 mg BID can be made. If the adverse event recurs despite the second dose reduction a final dose</p>

	<p>reduction to 100mg BD is permitted.</p> <p>Olaparib should be withheld in the event of:</p> <ul style="list-style-type: none"> • Grade 4 neutropenia • Grade 2-4 neutropenia with infection • Platelet count lower than $50 \times 10^9/L$ • Non-haematological toxicity grade 3 or greater, except nausea, vomiting or diarrhoea and fatigue associated with suboptimal pre-medication and/or management OR transient and clinically insignificant biochemical blood results. • Aspartate transaminase (AST) or alanine transaminase (ALT) elevations grade 3 or higher for more than 7 days. • Any other toxicity that, in the view of the principal investigator and the medical monitor, represents a clinically significant hazard to the patient until resolution of toxicity to no more than grade 1. <p>Biomarker Assessments:</p> <p>All patients enrolled in the study are required to have archival tumour tissue, fresh tumour biopsies, blood and urine samples collected during the study for the purpose of biomarker analyses including the following:</p> <ul style="list-style-type: none"> • Circulating tumour cells (CTCs): enumeration & molecular characterisation • PTEN and ERG immunohistochemistry (IHC) on primary tumour tissue and fresh paired biopsies • PTEN and ERG immunofluorescence (IF) in CTCs • <i>TMPRSS2-ERG</i> and <i>PTEN</i> fluorescence in situ hybridisation (FISH) studies in primary tumour, paired biopsies and CTCs • γH2AX and RAD51 foci formation in paired tumour biopsies and CTCs • Markers of tumour cell proliferation and cell cycle phase in paired tumour biopsies and CTCs • Circulating plasma tumour DNA • Circulating plasma tumour and whole blood RNA • Urine telopeptides and RNA • Proteomic profile • Metabonomic profile
<p>FOLLOW UP</p>	<p>Patients will be treated until disease progression (radiological progression) or withdrawal from the study for another reason. After discontinuing study treatment patients will be reviewed 30 +/- 5 days post cessation of treatment for an end of treatment safety assessment and 3 monthly for survival data.</p>

2 INTRODUCTION

2.1 Metastatic Castration Resistant Prostate Cancer

Prostate cancer is the second leading cause of male cancer-related mortality in the United Kingdom (1). While a proportion of patients have indolent disease, curable with local treatment, approximately a third of patients fail local treatment and develop incurable metastatic disease. Androgen deprivation therapy constitutes the mainstay of treatment for advanced prostate cancer. Most patients with advanced disease initially respond to hormonal deprivation therapy; however resistance inevitably develops within 1-3 years and represents a transition to more aggressive and invariably fatal disease. Recent studies have established that androgen signalling continues to play a pivotal role in tumour progression as castration resistance evolves. Androgen receptor (AR) gene amplification, AR overexpression, AR activating mutations and the presence of sufficient intratumoural androgen levels contribute to continued AR signalling despite a systemic castrate state. The recent emergence of the CYP17 inhibitor, abiraterone and other novel antiandrogens such as MDV3100 provide clinical validation that targeting AR signalling remains a useful approach in a significant proportion of CRPC patients (2, 3).

Metastatic prostate cancer is often associated with significant disease-related morbidity. The vast majority of these patients develop bone metastasis with clinical sequelae of bone pain, skeletal fractures, spinal cord compression and haematological compromise. In addition, soft tissue disease is liable to cause urinary obstructions and other problems.

Most CRPC patients have received multiple lines of hormonal manipulation prior to commencing chemotherapy for ongoing disease progression. Docetaxel and more recently cabazitaxel, Sipuleucel-T, alpharadin and abiraterone have demonstrated an overall survival advantage for metastatic CRPC (mCRPC) albeit of only several months (2, 4, 5, 6). Despite these important incremental advances in treatment options, benefits remain modest and the median survival of patients with mCRPC is unsatisfactory at approximately 18 – 36 months. It is clear that there is an urgent need for better treatments that offer durable clinical benefit and further improvement in overall survival for these patients.

Platinum Based Second-line Chemotherapy in Patients with CRPC

Platinum-based chemotherapy in Phase II trials has provided encouraging response rates (PSA and radiological) in the range of 44-60% and a median progression free survival (PFS) of 4-9.5 months in the post-docetaxel CRPC setting (7, 8). Likewise, satraplatin, an orally bioavailable platinum compound, has shown second-line antitumour activity in unselected patients in a Phase III trial, with a 50% PSA decline rate of 33% and a statistically significant PFS advantage in 40% of the patients (9). The lack of survival outcome in this study, despite the anti-tumour activity observed, may in part relate to inter-patient molecular heterogeneity and failure to optimally select the subgroup of tumours most likely to respond to this strategy.

Platinum salts induce interstrand and intrastrand DNA cross-links and consequently increased levels of double-strand (ds) DNA damage. Platinum compounds and PARP inhibitors (PARPi) exert their anti-tumour activity in a similar way by inducing increased ds-DNA breaks which overwhelms the DNA repair machinery in homologous recombination (HR) repair deficient tumours, consequently resulting in tumour cell death. Tumour sensitivity to the Poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib has been shown to correlate with prior platinum sensitivity in HR deficient, *BRCA1/2* mutant cancers (10, 11). It follows therefore that the previously established antitumour activity for satraplatin in prostate cancer supports the widely held premise that there is indeed a subgroup of CRPC that harbour HR DNA repair defects and will benefit from treatment with the PARP inhibitor, olaparib. No platinum is currently approved for the treatment of CRPC; indeed most CRPC remain platinum naïve. Recruitment of patients most likely to benefit based on biomarker driven molecular sub-classification is critically important for the successful development of novel therapies such as olaparib in this disease.

Prostate Cancer Heterogeneity: Clinical and Molecular

Prostate cancer is a highly heterogeneous disease with patients responding differently to treatments and overall having very different clinical outcomes. This is also reflected at a molecular level (12-16). Different molecular variants portend different clinical outcomes possibly secondary to distinct differences in molecular drivers. Despite this, to date, Phase III trials of novel anticancer drugs in this disease have failed to stratify patients on the basis of molecular profile and likely benefit. This inter-patient molecular heterogeneity may, in part, account for the high risk of failure of pivotal Phase III trials of anticancer drugs in this disease. We envision that an improved understanding of the biological and clinical significance of the molecular sub-classification of this disease will positively impact pivotal randomised clinical trials in this disease. The identification of primary tumour prognostic and predictive molecular markers as compared to the currently utilised suboptimal clinicopathological parameters will allow improved patient selection for optimal CRPC treatments thus maximising clinical benefit while avoiding unnecessarily exposure and toxicity in patients unlikely to benefit.

Dissecting Prostate Cancer Heterogeneity by FISH: *PTEN* & *ETS* Gene Rearrangements.

Functional Loss of *PTEN*

Prostate cancer can be molecularly sub-classified using multi-colour fluorescent in situ hybridisation (FISH). Dissecting the molecular profile of prostate cancers in this way has resulted in the characterisation of multiple commonly occurring genetic aberrations implicated in promoting tumour genesis (12, 15, 17, 18). The biological significance of gene rearrangements, deletions and amplifications as well as possible predictive and prognostic relevance are currently being extensively studied. Phosphatase and tensin homologue (*PTEN*), a tumour suppressor gene, negatively modulates the phosphatidylinositol 3-kinase (PI3)/AKT signal transduction pathway which fosters tumour growth, proliferation and survival (19-22). Bi-allelic and mono-allelic deletion of *PTEN* is a common event in prostate cancer and is implicated in tumour pathogenesis and progression (22-25). *PTEN* functional loss is associated with more advanced disease, higher-grade tumours and a worse clinical

outcome (15, 24-27). The frequency of reported *PTEN* inactivation in prostate cancer is variable in the literature, with mono-allelic and bi-allelic loss by FISH in the range of 30-68% (23, 26, 27, 28). Our own analysis has shown a complete loss of *PTEN* expression by immunohistochemistry (IHC) in archival tissue in approximately 50% in patients on the abiraterone phase I-II studies. The variability seen in the literature may be related to tumour stage, tissue processing, and IHC methodology. A recent study of tumour material from 59 patients with CRPC revealed that the *PTEN* gene was deleted in 77% of cases; 25% with homozygous deletions, 18% with homozygous and hemizygous deletions and 34% with hemizygous deletions. Bi-allelic *PTEN* loss was correlated with disease-specific mortality in this study (24).

Evidence for the importance of *PTEN* functional loss in prostate carcinogenesis also comes from transgenic studies. Critically, conditional *PTEN* loss in prostates from transgenic mice leads to the late development of metastatic prostate cancer (29). Prostate restricted overexpression and activation of *AKT*, however, resulted only in prostatic intraepithelial neoplasia (PIN) formation (30). These data suggest that *PTEN* loss may possibly induce prostate carcinogenesis not only through its phosphatase PI3K/*AKT* regulatory role but also possibly through its nuclear, DNA repair, role that has been recently reported (31, 32).

***TMPRSS2* Chromosomal Translocation**

Chromosomal translocation involving the androgen-responsive gene transmembrane protease serine 2 (*TMPRSS2*) with the oncogenic erythroblast transformation specific (*ETS*) transcription factor family of genes (*ETV1*, *ETV4*, *ETV5*) is reported in 50%-70% of prostate cancers (17, 33). *TMPRSS2/ERG* is the predominant type of gene fusion seen and results in overexpression of 3'-*ERG* sequence joined to the 5'-*TMPRSS2* promoter. Less frequently *TMPRSS2* becomes fused to *ETV1* and *ETV4*. *ERG* and other *ETS* family members are transcription factors that are implicated in the control of cell growth and differentiation. *TMPRSS2/ERG* fusion rearrangement has been shown to co-operate with *PTEN* haploinsufficiency to promote carcinogenesis (17, 22, 34) and accounts for continued hormone driven disease (35). Recent evidence implicates topoisomerase IIB-mediated DNA breakage during the induction of transcriptional programs in generating these *TMPRSS2/ERG* fusion rearrangements (36, 37, 38).

We have utilised validated FISH assays to evaluate *PTEN* deletions and the commonest *ETS* gene rearrangements (*ERG* and *ETV1*) on the Trans-Atlantic Prostate Group (TAPG) tissue microarray (TMA) (15). We demonstrated that patients with *PTEN* loss (heterozygous or homozygous: 17% of newly diagnosed cancers) had significantly worse cause-specific and overall survival compared with patients with no *PTEN* loss, supporting the haploinsufficiency proposed for the *PTEN* gene (Figure 1). Three hundred and eight patients with both *ETS* gene (*ERG* and *ETV-1*) rearrangement and *PTEN* loss status available were analysed for survival outcome (Figure 2). The largest group of patients (n=167, 54%) had no *ERG* or *ETV-1*-gene rearrangement and no *PTEN* loss and had the best outcome with 85.5% survival at 11 years. A poor prognosis group was also identified (n=19, 6%) who had *PTEN* loss but no *ERG* or *ETV-1*-gene rearrangement with a cause-specific survival of 13.7% at 11 years and a median survival of 5 years from diagnosis. Patients with an *ETS* gene rearrangement with or without *PTEN* loss had an intermediate prognosis in keeping with the hormonal sensitivity of these cancers, which has recently

been described (15, 27). Overall, therefore, these data indicate that prostate cancer is a molecularly heterogeneous disease, with cancers demonstrating PTEN loss having a poor outcome, and that to accelerate the successful development of targeted therapies in CRPC, identifying the appropriate subgroup of patients most likely to benefit is paramount.

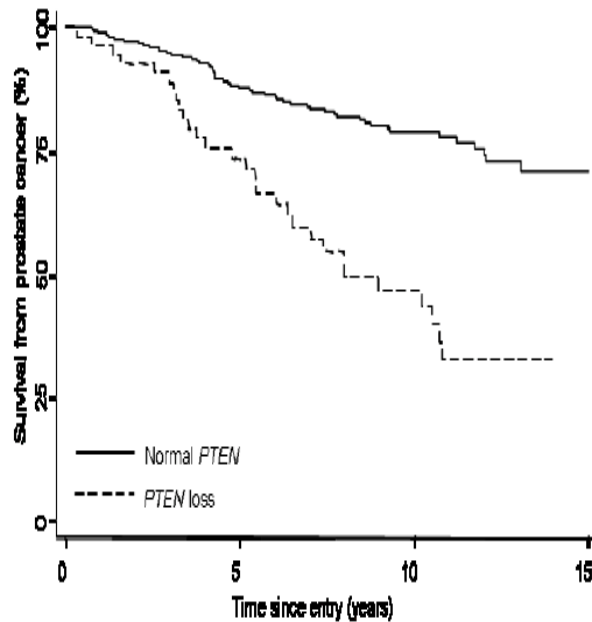


Figure 1: PTEN loss prostate cancers have a worse overall survival

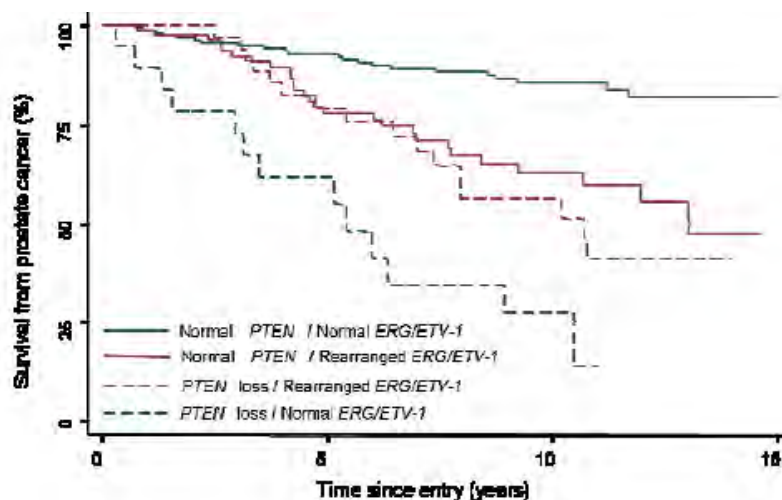


Figure 2: Multi-colour FISH based stratification by studying *ETS* rearrangements and PTEN loss.

PTEN Loss, *ETS* Gene Rearrangements and HR Repair Defects

PTEN is implicated in many functions, both PI3K/AKT dependent and independent. Recent reports suggest in addition to lipid phosphatase function, PTEN localises to the nucleus and that its function includes maintenance of genomic stability (31, 32) by a number of mechanisms including interacting with CENP-C an integral centromeric binding and

stabilising protein, regulating the transcription of RAD51, a critical DNA double strand break (DSB) repair protein (39) and modulating cell cycle progression (40).

PTEN loss results in impaired HR DNA repair with reduced RAD51 expression, increased chromosomal aberrations and genomic instability (31,39). Moreover, in vitro cell-based experiments and in vivo xenograft studies have established that PTEN deficient tumour cells much like *BRCA1/2* deficient tumours are selectively sensitive to platinum compounds and potent PARP inhibitors including olaparib (41-43). Furthermore, restoration of PTEN expression in PTEN deficient tumour cell lines restores PARP inhibitor resistance, confirming PTEN as a determinant of the response to PARP inhibition. This synthetic lethal relationship between PTEN-null tumours and PARP inhibition supports the therapeutic utility of PARP inhibitors in PTEN-deficient tumours. Moreover, *ERG*, the oncogene driven by the commonest prostate cancer genetic driver lesion *TMPRSS2/ERG*, has been shown to directly associate with PARP and requires PARP for its transcriptional regulatory function with PARP inhibition having antitumour activity in *ERG* rearranged tumour models (44,45).

Given these pre-clinical observations and the putative role of PTEN in maintaining chromosomal stability, we predict that tumours with PTEN loss and /or *ETS* gene rearrangements are likely to be hypersensitive to PARP inhibition. We therefore aim to evaluate the antitumour activity of olaparib in patients with sporadic CRPC using an adaptive biomarker driven design to identify and clinically qualify predictive biomarkers of olaparib sensitivity for optimal patient selection.

2.2 PARP and PARP Inhibition

Poly(ADP-ribose) polymerase 1 (PARP-1) is a zinc-finger DNA-binding enzyme that is activated >500 fold upon binding to DNA double or single strand breaks (46). PARP-1 (113 kDa) and PARP-2 (62 kDa) are thus far the only members of the PARP enzyme family known to be involved in DNA damage signalling and repair with a degree of functional redundancy between these proteins. PARP-1 signals the presence of DNA damage and plays a critical regulatory role in DNA damage repair. PARP-1 is involved in a wide range of cellular processes including DNA repair and maintenance of genomic integrity, regulation of protein expression at the transcriptional level, regulation of cellular replication and differentiation, regulation of telomerase activity, and involvement in the cell apoptotic pathway (47).

PARP-1 comprises 3 domains, the N-terminal DNA-binding domain containing 2 zinc fingers, the auto-modification domain and the C-terminal catalytic domain. PARP-1 binds to both single and double-stranded DNA breaks through the zinc-finger domain and catalyses the cleavage of nicotinamide adenine dinucleotide (NAD)⁺ into nicotinamide and ADP-ribose, and subsequently transfers successive units of ADP-ribose onto DNA, histones, PARP-1 and other DNA repair proteins to form branched ADP-ribose polymers. These branched ADP-ribose polymers result in post-translational modification of histones and other nuclear proteins which convert the DNA damage signal into intracellular signals that activate either DNA base-excision-repair (BER) pathways or cell death if the damage is beyond repair. Other transcriptional factors and signalling molecules are also poly-ADP-

ribosylated by PARP-1 to initiate a multitude of other important cellular functions (47,48). Given the critical role that PARP plays in single strand DNA repair it is not surprising that PARPi are able to potentiate the cytotoxic damage incurred with DNA-damaging chemotherapy agents and ionizing radiation (49). PARP inhibitors have also shown significant single agent activity in tumours with HR deficiency (10,11, 50,51).

Synthetic Lethality Between *BRCA1/2*-mediated Homologous Recombination Repair and PARP-1

Abrogating PARP dependent BER, which is responsible for repairing DNA single strand breaks (SSBs) results in the accumulation of SSBs. These SSBs collapse at the replication forks during DNA synthesis giving rise to double strand breaks (DSBs) that are detrimental to the cell. The DNA DSBs are preferentially repaired by high fidelity HR repair that restore genomic integrity under normal circumstances. *BRCA1* and *BRCA2* genes encode proteins that are essential in HR repair. *BRCA1/2* deficient tumour cells lack HR repair capacity and are therefore unable to repair these replication associated DSB DNA damage, which accumulates in the context of suppressed PARP activity, leading to chromosomal instability, cell cycle arrest and apoptosis. The profound selective sensitivity of *BRCA* deficient tumour cells for PARPi compared with unaffected heterozygous mutant normal tissue retaining one functional *BRCA* allele provides a large therapeutic window (47,52,53).

Preclinical models have demonstrated that HR deficient tumour cells with *BRCA1*^{-/-} and *BRCA2*^{-/-} genotype are exquisitely sensitive to PARP inhibition with olaparib (previously referred to as KU-0059436 or AZD2281 in earlier studies), in contrast to heterozygous mutant or wild-type cells (52). Likewise, in the clinic, olaparib is an efficacious therapy with durable antitumour activity and a favourable toxicity profile in HR deficient tumours arising in *BRCA1* and *BRCA2* mutation carriers including several patients with mCRPC (11).

Epigenetic Disruption of *BRCA 1/2* Function and Other Causes of HR Impairment

It has been hypothesised that targeting SSB DNA repair with PARPi will be a useful therapeutic strategy in sporadic tumours that harbour HR repair defects. This may occur due to either epigenetic or genetic silencing of *BRCA1/2* function or disruption of any of the other key proteins that make up the HR repair pathway. Loss of *BRCA 1/2* function may arise spontaneously via somatic mutations and epigenetic mechanisms during tumour formation. These somatic mechanisms of *BRCA1/2* functional loss are increasingly implicated in sporadic carcinogenesis (54,55). Epigenetic gene silencing of tumour-suppressor genes is a well-recognised phenomenon with methylation of the *BRCA1* promoter found in 11-14% of sporadic breast cancers and 5-31% of ovarian cancers (56). Epigenetic modification of the Fanconi anaemia/*BRCA* pathway through promoter hypermethylation in lung, oral cancer and cervical cancer cell lines render these cells highly sensitive to DNA cross-linking agents (57,58). Somatic mutations of *BRCA* genes and heterozygous loss also appear to be more common than previously defined (54,58,59). The term "BRCAness" is commonly used to describe the phenotypic likeness of a sporadic tumour with a familial-*BRCA1/2* mutation related cancer (56). Identification of this BRCAness phenotype secondary to epigenetic / genetic silencing of the Fanconi anaemia/*BRCA* pathway may select for clinical benefit from PARPi in these sporadic cancers.

In addition to somatic *BRCA1/2* dysfunction, disruption of any of the other critical proteins that make up the HR repair pathway such as RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHEK1, CHEK2, FANCD2, FANCA or FANCC 2 have been shown in preclinical models to cause HR deficiency and render these tumour cells highly susceptible to synthetic lethality with PARPi (56, 60, 61).

Clinical evidence supporting single agent olaparib antitumour activity in sporadic cancer was recently reported (58,62,63), with durable objective responses observed in 28% of sporadic high grade serous ovarian cancers in one study and a further study reporting a significant improvement in progression free survival (62,63). These responses may be explained in part by the high frequency of somatic mutations of *BRCA1/2* as well as epigenetic silencing of this and other key HR genes in high grade serous ovarian cancer (58). These results have led to the further evaluation of single agent olaparib in other tumour types enriched for HR defects. Identifying the subgroup of sporadic tumours with HR defects through validated predictive biomarker studies is imperative, if we are to successfully develop novel treatments such as PARP inhibitors (PARPi) and personalise medicine.

There has been limited investigation to date of the incidence of somatic aberrations in key HR related genes in advanced prostate cancer. High penetrance germline mutations in several candidate genes involved in DSB repair including *BRCA1*, *BRCA2*, *CHEK2*, *BRIPI/FANCI* and *NBS1* are known to account for a small fraction of prostate cancer cases (64-70). *PTEN* however is one of the commonest tumours suppressor genes that is deregulated in prostate cancer and is implicated in the pathogenesis of this tumour as discussed above. Loss of *PTEN* function may also result in deficient HR DNA repair with reduced RAD51 expression and sensitivity to PARP inhibition (39,41). Likewise, the *ERG/TMPRSS2* gene rearrangement which is observed in 50% of prostate cancers is also implicated in conferring sensitivity to PARPi (44). Overall, these data support the evaluation of PARP inhibitors in the treatment of advanced prostate cancer.

2.3 Rationale for Study

Despite recent advances in CRPC treatment, metastatic prostate cancer remains a common disease with a poor outlook. Improved treatments that offer durable clinical benefit and significant survival impact remain an area of unmet medical need. As with most chemotherapies, a proportion of prostate cancers will not respond due to the underlying tumour biology and inherent resistance mechanisms. Understanding the underlying molecular determinants of response and resistance to different treatments is critical for improvement in CRPC patient outcome through optimally selected treatments.

The previously established antitumour activity of platinum based regimens in advanced prostate cancer suggests that there is a subgroup of CRPC susceptible to DNA damaging agents such as platinum and PARPi.

The PARP inhibitor, olaparib is a novel anticancer agent with strong preclinical and clinical data for significant antitumour activity in HR repair deficient tumours arising in *BRCA1* and

BRCA2 mutation carriers including a number of patients with metastatic CRPC (10,11,50,51,52,53). Recent clinical evidence supports the utility of this approach in sporadic high-grade ovarian cancers enriched for HR defects (62,63). Moreover, there is a growing body of preclinical evidence that supports extending this approach to a wide range of other sporadic tumours with disruption to other non-redundant components of the HR repair pathway including RAD51 and other essential HR repair proteins (60,61). Identifying these sporadic tumours with HR repair defects through validated predictive biomarkers remains a challenge and focus of ongoing research.

PTEN loss has been implicated to confer HR DNA repair defects with reduced RAD51 expression, increased genomic instability and tumour sensitisation to PARP inhibition (41-43). Homozygous *PTEN* loss by FISH is present in 20-30% of CRPC, with loss of protein expression by IHC being far more common (21). In addition, the *TMPRSS2/ERG* driver rearrangement, which is present in approximately 50-60% of prostate cancers and co-associates with *PTEN* loss has also been reported to confer sensitivity to PARP inhibition (44,45).

The target population for this trial are patients with advanced metastatic CRPC progressing following docetaxel treatment. A proportion of patients may also have received treatment with abiraterone and cabazitaxel. Given the high prevalence of loss of *PTEN* function and *TMPRSS2/ERG* rearrangements in this population and the strong preclinical rationale for this therapeutic strategy, we anticipate that a subgroup of these patients will benefit from olaparib treatment.

Patients may continue olaparib treatment until disease progression or treatment intolerance. Patients may however withdraw from the study at any point if they choose to do so or if the investigator believes it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for reducing the dose of olaparib are provided.

Rationale for Circulating Tumour Cell Based Studies in CRPC

Enumeration of circulating tumour cells (CTC) number using the Cell Search system (Veridex, PA) is a valid biomarker to monitor the effectiveness of therapy of patients with metastatic breast cancer (71-73), colorectal cancer (74) and prostate cancer (75-78). High baseline counts have consistently been associated with more aggressive disease and a worse outcome (76-78). CTC counts are highly prognostic for overall survival, and CTC count falls post-treatment associate with an improved overall survival and response to therapy in CRPC. In a pilot study, univariate analysis demonstrated that CTC counts of $< 5/7.5$ ml blood or $\geq 5/7.5$ ml blood correlated with OS (0.002; HR=7.37); in multivariate analyses CTC counts and PSA doubling time were the only 2 independent predictors of outcome unlike PSA, Gleason score, presence and absence of bony metastasis and age (75). In a similar study that related changes in CTC counts in patients with CRPC during the first 2 cycles of treatment with clinical outcome, we observed that patients with CTC counts that remained below 5 cells/7.5 ml blood during treatment with cytotoxic therapy had the best outcomes, whilst patients whose counts changed from $\geq 5/7.5$ ml blood to ≤ 5 had improved outcomes compared to the patient cohort whose CTC count remained persistently

elevated at $\geq 5/7.5$ ml blood throughout treatment. In addition, patients whose CTC counts increased during treatment from < 5 to $\geq 5/7.5$ ml blood had a similar poor outcome to the group whose count remained persistently elevated at ≥ 5 CTCs throughout treatment suggesting the development of treatment resistance (76). CTC counts were commonly detected in patients with advanced CRPC; CTC counts $>5/7.5$ ml were detected in 19/49 (39%) and 21/28 (75%) of chemotherapy naïve and post-docetaxel patients respectively treated on the phase I-II Abiraterone studies (35). We now have data from almost a thousand patients participating in the randomised Phase III abiraterone trial (COU-301) that CTC conversion from ≥ 5 to <5 as well as any fall in CTC from 10% to 90% count post-treatment at 1, 2, 3 months after starting abiraterone is a statistically robust surrogate/intermediate endpoint of overall survival, meeting all of Prentice's criteria for surrogacy (78)

In addition, CTCs have been shown to retain many of the genomic characteristics of the primary tumour and thus provide a useful opportunity to study molecular changes in the disease profile longitudinally with ongoing treatment. Multicoloured FISH assays have been successfully applied to determine commonly found genomic alterations such as AR amplification, *PTEN* deletions and *TMPRSS2/ERG* fusion rearrangements in prostate CTCs (35,79,80). We have also developed multiplex immunofluorescence assays to evaluate protein expression in CTCs.

Rationale for Radiographic PFS and 6 months PFS as an Endpoint

Clinical research in prostate cancer has been hindered by the difficulty in objectively defining cancer progression. Composite endpoints that include patient reported, radiographic, and skeletal-related events have suffered from subjectivity. Conventional RECIST alone has limitations in CRPC in defining radiographic progression due to the fact that fewer than 50% of men with CRPC have measurable lesions greater than 2cm in size, and most of these lesions are in lymph nodes which impact survival less than visceral metastases (81). Conventional RECIST also lacks the sensitivity to differentiate true progression of bone metastasis from the flare phenomenon on bone scan or CT scan due to healing of previous bone metastasis (82,83). Although radiographic PFS is not a surrogate for overall survival in patients receiving docetaxel therapy, it outperforms PSA based progression (83).

Attribution of disease progression due to tumour flare phenomenon will be mitigated in this study by applying the new consensus guidelines that requires a confirmatory bone scan at least six weeks after the original scan to define progression. This will reduce the number of false positive determinations of CRPC progression. (Refer to Appendix D)

Progression of metastatic bone disease is of paramount importance to CRPC patients since it is responsible for severe morbidity of skeletal related events such as fracture, pain, and spinal cord compression. Similarly, progression of soft tissue metastasis may be associated with clinically significant morbidity. Prevention or delay in cancer progression should result in clear clinical benefit to the patient. In conclusion, radiologic PFS (rPFS) is an objective measurement that may associate with clinical benefit in the proposed study population.

Pain and Analgesic Assessments

Pain due to bone metastases and nerve root compression is a common experience for patients with advanced prostate cancer. Pain has previously been shown to significantly associate with overall survival in advanced prostate cancer. The McGill Pain Questionnaire (MPQ) (PPI score 0-2 versus 3-5) successfully stratified the survival of first line chemotherapy patients in TAX 327 (84,85).

The BPI-SF, a numeric rating scale (NRS), has been selected as the pain instrument for this study due to the high correlation of numeric rating scales with verbal descriptor scales (e.g. MPQ PPI) (86) and its prior use in other metastatic prostate cancer studies (87,88). The BPI-SF assesses both the intensity of pain and the interference in the patient's function caused by their pain (89). The BPI-SF data can potentially help illustrate the overall benefit of treatment on pain. Analgesic usage will be scored according to the WHO analgesic ladder: 0 for no analgesic, 1 for non-opioid analgesics (including NSAIDs, paracetamol/acetaminophen, antidepressants, and agents intended to treat neuropathic pain), 2 for opioids for moderate pain, and 3 for opioids for severe pain (90).

3 BACKGROUND THERAPEUTIC INFORMATION

Olaparib

Olaparib previously referred to as AZD2281 or KU-0059436 in earlier studies is a potent inhibitor of PARP-1. Olaparib shows significant monotherapy activity in tumour cells with defective components of HR, such as cells with the *BRCA1* *-/-* and *BRCA2* *-/-* genotype both preclinically and clinically (10,11,50,51,52,53,62,63). Selective tumour sensitivity to this PARP inhibitor has also been observed in tumour cells with loss of PTEN function and *ETS* gene rearrangements (41,42,44). This sensitivity in pre-clinical models is expected to translate to clinical benefit.

3.1 Pre-clinical Experience with Olaparib

This pre-clinical and clinical experience with olaparib (AZ2281, KU0059436) is fully described in the Investigator Brochure (IB). Key findings are summarised below.

Pharmacokinetic Data

The olaparib molecule shows cellular activity in the low nM range with a cellular dose for 50% inhibition (IC50) of 2 nM in HeLa cells. Distribution of olaparib is typical for an orally administered foreign compound, in the gastro-intestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. The oral bioavailability of olaparib when dosed at 5mg/kg via a solution formulation was 17% and 19% in male and female rats and 79% \pm 12 in male dogs. An oral study of olaparib demonstrated bioavailability of >85% for both 5% and 20% w/w microionised dispersion of the drug substance in Gelucire. Following single oral dosing (5mg/kg), absorption was rapid with an AUC of 10.3 \pm 2.01 in

dogs. The estimated $t_{1/2}$ for olaparib was 3.0, 2.5 and 4.61 \pm 1.66 hours in female rats, male rats and dogs respectively. Multiple oral dosing of olaparib in 28-day rat and dog studies demonstrated that absorption was rapid and exposure increased greater than proportionally with dose across the dose range examined (upto 15mg/kg/ day in dogs and upto 40mg/kg in rats). Plasma protein binding of olaparib varied between 70.4% and 58.8% in rat and dog studies. Metabolism data to date is limited and further investigations are ongoing. To date, several metabolites have been observed in pre-clinical studies. Similar metabolite profiles were observed in the urine and faeces of male and female rats. Excretion is primarily via the faeces and to a lesser extent, the urine. In a study of [14 C]-olaparib in the rat, excretion was 76 \pm 13% in faeces and 20 \pm 11% in urine. For more detailed preclinical data please refer to the IB.

Toxicology and Safety Data

Olaparib has shown comparatively low toxicity in rodent and dog toxicology studies. Oral doses of olaparib were well tolerated for up to 6 months in safety studies and showed no cardiovascular, respiratory, central, peripheral and autonomic nervous system toxicity findings that were a concern. The toxicology studies indicate that the target organ of toxicity is the bone marrow. Specific *ex vivo* work has been conducted exposing human bone marrow cells to olaparib, which has confirmed that olaparib is also active against human bone marrow. The cytotoxic effect becomes evident at a higher concentration than that which fully ablates PARP activity (mean IC₅₀ of 2.7 μ M for myelosuppression [n = 4 human donors] compared with 0.1 μ M for total PARP-1 activity inhibition). These data, along with the 28-day dog and rat studies, show a myelotoxic effect that is mild-to-moderate and is reversible. Platelets appear first affected, followed by white blood cells. Importantly, oncology clinics are used to monitoring for the onset of such effects and are expert in their management.

Olaparib showed no mutagenic potential in the Ames test. Olaparib was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test, and was genotoxic in the rat micronucleus test. Reproductive toxicology data indicate that olaparib can have adverse effects on embryofetal survival and development at dose levels that do not induce maternal toxicity. These findings are not uncommon for many therapeutic agents used in oncology, and so do not present an unacceptable risk when appropriately clinically managed. For further details on these tests or on the fertility studies please refer to the IB.

3.2 Clinical Experience with Olaparib

3.2.1 Pharmacokinetic (PK), Pharmacodynamic (PD) Data

In the Phase I study, patients with solid tumours were given olaparib at a starting dose of 10mg for the first 14 days of a 21-day cycle with a subsequent protocol amendment, changing the dose schedule to continuous daily dosing starting at 100 mg BID for a 28-day cycle. Absorption was rapid and a peak plasma concentration was observed between 1-3 hours post dosing with a terminal elimination half-life of 6.10 hours, supporting twice daily dosing. Drug exposure increased dose proportionally with doses up to 100 mg but increase less than dose proportionally thereafter. The mean volume of distribution and mean plasma

clearance are approximately 40.3 L and 4.55 L/h. On multiple dosing, there was no evidence of any time dependency of the PK and no marked accumulation. Exposure increased proportionally with dose at doses up to 100 mg twice daily but increased in a less than proportional fashion at higher doses. There was no evidence of any marked ethnic difference in PK of olaparib between Japanese and Caucasian patients. Following dosing to cancer patients at doses of 400 mg BID, the population estimated maximum plasma concentration at steady state ($C_{max\ ss}$) ranged from 1.45 $\mu\text{g}/\text{mL}$ to 11.0 $\mu\text{g}/\text{mL}$ (3.34 μM to 25.3 μM , equivalent to unbound concentrations of 0.26 $\mu\text{g}/\text{mL}$ to 1.99 $\mu\text{g}/\text{mL}$ [0.6 μM to 4.58 μM]); the steady state area under the plasma concentration-time curve (AUC) (area under plasma concentration-time curve from zero to 12 h [AUC₀₋₁₂]) ranged from 6.56 $\mu\text{g}\cdot\text{h}/\text{mL}$ to 122 $\mu\text{g}\cdot\text{h}/\text{mL}$.

The distribution of olaparib is typical for an orally administered compound, in the gastrointestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Following administration of a radiolabelled dose of olaparib to cancer patients, olaparib accounted for approximately 70% of the circulating material in the plasma with the remainder accounted for by 3 other components (each accounting for approximately 10% of the material), all of which were also present in the excreta. Drug-related material was eliminated in the urine (35% to 50%) and in the faeces (12% to 60%) with 10% to 20% and 0.6% to 14% of the dosed material recovered in the urine and faeces as unchanged drug, respectively. A further 35 and 19 drug related components were excreted in the urine and faeces, respectively. The metabolites produced were predominantly a consequence of hydroxylation, oxidation or dehydrogenation of the piperazine carboxycyclopropyl, the flourophanyl and the phthalazinone ring system.

Evidence of inhibition of PARP-1 activity has been seen in peripheral blood mononuclear cells (PBMC) and tumour samples from patients dosed with olaparib at all dose levels studied (10 mg to 600 mg) but the data shows wide inter-individual variability in the extent of inhibition achieved and no evidence of any relationship between extent of inhibition and dose administered. Concentration-response curves for inhibition of PARP-1 activity in both PBMC and tumour samples have been generated from a population PK-PD analysis of the data. The population average maximal extent of inhibition in PBMC and tumour samples were 50.6% and 70%, respectively, with maximal inhibition achieved at plasma exposures (steady state AUC) in excess of 1 $\mu\text{g}\cdot\text{h}/\text{mL}$ (exposures which would be expected to be reliably achieved following doses of >40 mg). The potential clinical benefit of continuous dosing is supported by preclinical studies, which show that tumours re-grow after short-term use (e.g. 14 days) and that continuous PARP inhibition with olaparib was able to prevent tumour re-growth. The maximum tolerated dose of olaparib established in the Phase I trials was 400 mg twice daily, continuously (10).

3.2.2 Efficacy Data

The phase I study was enriched with *BRCA1* and *BRCA2* mutation carriers with advanced tumours in the escalation and expansion phase given the strong preclinical rationale of selective tumour killing in *BRCA1/2*-deficient cell lines. In the Phase I study, 41% of 46 evaluable patients with *BRCA*-mutant ovarian cancers achieved objective responses

(complete or partial responses) either by Gynecologic Cancer Intergroup (GCIG) CA125 or RECIST criteria and a further 11% of patients attained RECIST disease stabilisation (10,11). The encouraging clinical benefit rate of >50% in the subpopulation of *BRCA1/2* mutation cancer patients provides compelling evidence of single agent PARP inhibitor activity in *BRCA*-deficient cancer patients. Durable antitumour responses have also been reported in *BRCA* mutated breast and prostate cancer patients with one prostate patient ongoing treatment for more than 2 years (10, 11, 50, 51).

Two parallel open-labelled multicentre phase II studies of olaparib in *BRCA1/2* mutation carriers with advanced breast and ovarian cancer have confirmed the significant therapeutic efficacy of PARPi in this population (50, 51). 54 breast cancer patients and 56 ovarian cancer patients with advanced heavily pre-treated disease were recruited to 2 non-randomised sequential dose cohorts of 400mg and 100mg BID of olaparib. Following efficacy assessment of the 2 dose levels; patients on the 100mg BID cohort in both studies were allowed to increase the dose of olaparib to 400mg BID given the improved antitumour activity seen at the higher dose level. The breast cancer study reported an objective response rate (ORR) of 41 % (11/27) with 1 complete response (CR) and 10 partial response (PR)s and a median progression free survival (PFS) of 5.7 months (m) (range 4.6-7.4m) at 400mg BID in contrast to an ORR of 22% (6/27) with 6 PRs and a median PFS of 3.8m (range 1.9-5.5m) at the lower dose level (27). In the ovarian study, patients on the 400mg BID and 100mg BID dose levels showed an ORR of 33% (11/33) versus 13% (3/24) by RECIST criteria, a response by either RECIST or by GCIG criteria of 61% (20/33) versus 17% (4/24) and a median duration of response of 290 days (range: 126-513 days) versus 269 days (range:169-288 days) respectively (50). Both dose levels demonstrated clinical activity, however the 400mg BID was more efficacious with improved outcomes establishing substantial antitumour activity for olaparib at a dose of 400mg BID in heavily pre-treated, *BRCA* mutant advanced breast and ovarian cancer patients (50,51). A further phase II study of olaparib at 400mg BID in patients with sporadic high grade ovarian cancer showed an objective response rate of 28%. This study provided the first clinical evidence for the antitumour activity of olaparib in sporadic serous ovarian cancers (62). Most recently, patients with sporadic platinum sensitive serous ovarian cancer who previously achieved either a partial or complete response from platinum therapy demonstrated a doubling of the progression free survival (PFS) from 4.8months to 8.4months with 400mg BID olaparib maintenance treatment compared to placebo. The hazard ratio (HR) was 0.35 (95% CI: 0.25, 0.49; p<0.00001) (63).

3.3 Summary of Clinical Toxicity Data

The clinical experience with olaparib is fully described in the IB and largely has been conducted with the Gelucire® 44/14 (capsule) formulation.

As of 20 May 2011, 1645 patients suffering from ovarian, breast and a variety of other advanced solid tumours had been exposed to olaparib across the dose range 10 mg daily to 600 mg BID, either as monotherapy (n=12 studies) or in combination with other chemotherapy agents (liposomal doxorubicin, cisplatin, dacarbazine, gemcitabine,

gemcitabine+cisplatin, carboplatin, carboplatin+paclitaxel, paclitaxel, topotecan, irinotecan, or bevacizumab).

Data from these studies indicate that olaparib is generally well tolerated at doses up to 400 mg BID as monotherapy in patients with solid tumours. Administration of olaparib has been associated with laboratory findings and/or clinical diagnoses of:

- Haematological toxicity:
 - Anaemia, generally mild to moderate (CTCAE grade 1 or 2)
 - Neutropenia, predominantly mild to moderate (CTCAE grade 1 or 2)
 - Thrombocytopenia, generally mild to moderate (CTCAE grade 1 or 2), sometimes severe (CTCAE grade 3 or 4)
 - Mean corpuscular volume or elevation, generally mild to moderate (CTCAE grade 1 or 2)
- Nausea and vomiting, generally mild to moderate (CTCAE grade 1 or 2), intermittent and manageable on continued treatment
- Dyspepsia, generally mild to moderate (CTCAE grade 1 or 2)
- Dysguesia, generally mild to moderate (CTCAE grade 1 or 2)
- Fatigue, generally intermittent of mild to moderate intensity (CTCAE grade 1 or 2)
- Headache, generally mild to moderate (CTCAE grade 1 or 2)
- Dizziness, generally mild to moderate (CTCAE grade 1 or 2)
- Pneumonitis events with no consistent clinical pattern have been reported rarely in a small number of patients
- Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML) have been reported very rarely in a small number of patients

From the completed studies, there are no safety concerns noted for the renal or hepatic parameters measured and no clinically significant changes of concern relating to coagulation parameters. The changes in haematological parameters (haemoglobin, neutrophils, and thrombocytes) are as expected for olaparib monotherapy or can be explained by co-existing conditions/previous chemotherapy.

Olaparib appears to be generally well tolerated at PARP inhibitory dose levels in the monotherapy clinical studies with predominantly mild toxicity. Thus it represents a potential

advance in the treatment of advanced cancers by directly inhibiting PARP-1 and hence tumour growth as monotherapy.

Preliminary data from Phase I and Phase II studies of olaparib in combination with various chemotherapy agents indicate a substantial increase in neutropenia, thrombocytopenia and anaemia compared to giving these cytotoxic agents alone. These findings are consistent with pre-clinical findings. There are more severe haematological events i.e., CTCAE grade 4 neutropenia, febrile neutropenia and thrombocytopenia being reported as SAEs. When these toxicities occur it has been managed with routine clinical practise, including dose delays, dose reductions and intermittent doses and/or the use of supportive care measures such as G-CSF.

Final laboratory data from D0810C00002 (KU36-92) study have shown mean corpuscular volume (MCV) increases in approximately 30% of patients in the study, especially with prolonged treatment with olaparib (≥ 6 cycles of treatment). The MCV elevations were mild to moderate in intensity, observed in the 200 mg BID dose cohort and above and were asymptomatic in nature. There was no obvious correlation of MCV with haemoglobin, platelets or white blood cell (WBC) values for these patients, and there does not appear to be any clinical consequences. MCV has not been captured as a standard laboratory parameter within the olaparib Phase II studies D0810C00008 (KU36-44) and D0810C00009 (KU36-58), however elevations in MCV were also observed in a number of patients from these studies. The MCV elevations again appear to become progressively elevated over time. Elevations in serum amylase were observed in approximately 15% of patients from final laboratory study data from D0810C00002 (KU36-92). The majority of these increases (13%) were mild to moderate (CTCAE grade 1 or 2) with no apparent link to clinical symptoms. No new significant safety information has emerged from any other reported studies with respect to elevations in serum amylase.

Rare Adverse Events

Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML)

As of May 2011 there have been 5 reports of MDS and 4 reports of AML in a total of 6 patients (0.36%) from 5 monotherapy studies out of a total of 1645 patients. Additionally, there has been a further report in one patient out of 294 patients that received olaparib or the comparator (0.34%), in this case pegylated liposomal doxorubicin. The 6 patients received between 6 months and 32 months of olaparib treatment prior to the diagnosis of MDS/AML. In all 6 cases there were other contributory factors that may offer an alternative explanation for the development MDS/AML. All but one patient were also known to be *BRCA1/2* mutations carrier, another factor that may predispose them to developing MDS/AML. Five of the 6 patients with MDS/AML had other cancers that preceded the diagnosis of ovarian/peritoneal cancers. The ovarian/peritoneal cancer was diagnosed between 2 to 12 years before these patients were commenced on olaparib treatment. These patients were heavily pre-treated with multiple agents including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents over a long duration of time (2 to 17 years) prior to starting olaparib treatment. One patient had a family history of leukemia. Four of the 6 patients have died one from MDS, two from AML and one from disease progression. For 2 of these patients, the MDS/AML syndrome was diagnosed post

completion of olaparib treatment. Epidemiological studies indicate that the incidence of AML/MDS is in the range of 7-8% in ovarian cancer patients who received prior alkylating agents at the 5 year mark (91) and 0.4% at the 2 year mark in first line ovarian cancer patients (92). The cumulative risk of AML/MDS observed with olaparib treatment is in line with the rate quoted at the 2 year mark for first line ovarian cancer patients.

Pneumonitis

As of May 2011 there have been 7 (0.42%) reported cases of pneumonitis or suspected pneumonitis from a total of 1645 patients. Three were from monotherapy studies and 4 were from combination studies (3 from olaparib + liposomal doxorubicin and 1 from olaparib + topotecan). These patients had a variety of cancer types including breast cancer, nonsmall cell lung cancer, small cell lung cancer and cancer of the thymus. All but one of these patients were hospitalised for the management of pneumonitis. Five of these patients have died; 2 from pulmonary insufficiency and 3 for disease progression. In summary, the 7 reported cases of pneumonitis presented with no consistent clinical pattern and were heavily confounded by a number of predisposing factors (including disease under investigation, underlying pulmonary disease, pre-existing medical conditions, smoking history and/or previous chemotherapy and radiotherapy). The frequency of pneumonitis seen with olaparib treatment is consistent with the expected rates of pneumonitis in a cancer population (93-94).

Pre-clinical and Clinical Experience with New Melt-Extrusion (tablet) formulation

Melt-Extrusion (tablet) formulation has been developed to render the olaparib amorphous and presents the drug in a solid dispersion in copovidone (30% drug loading). The milled extrudate is then blended with pharmacopoeial excipients and compressed into a tablet.

The Melt-Extrusion (tablet) formulation, when dosed to fasted dogs at a 100 mg dose, shows at least 2.4 times the C_{max} & AUC than the Gelucire® 44/14 (capsule) formulation. In addition the Melt-Extrusion (tablet) formulation showed reduced pharmacokinetic variability in the dog with CV of ~ 20% as compared to ~ 50% for the Gelucire® 44/14 (capsule) formulation. It is envisioned that the new Melt-Extrusion formulation of olaparib should provide a more bioavailable and patient friendly formulation by minimising the number of dosage units and providing a more consistent PK profile.

This olaparib Melt-Extrusion formulation (tablet) will be the formulation evaluated in the Phase III clinical programme and consequently this study will also be conducted with the olaparib tablet. There is an ongoing trial (D0810C00024) being conducted at the Royal Marsden NHS Foundation Trust and other centres to establish the comparative bioavailability of the tablet formulation compared with the capsule formulation. In addition single and multiple dose safety & tolerability data will be gathered.

Following single oral dosing with the tablet formulation, absorption was more rapid than the capsule. The C_{max} was typically achieved between 0.5 hours and 2 hours after dosing. Following the peak, plasma concentrations declined biphasically with the mean terminal $t_{1/2}$ of 6.97 hours. The mean volume of distribution of olaparib tablet was 54.9L and the mean

plasma clearance was 542L/h. Both G_{mean} , C_{max} and AUC increased approximately proportionally with dose (8-fold and 12-fold, respectively, for a 10-fold increase in dose).

The relative bioavailability (BA) of the tablet formulation (compared to capsule) at the 3 lower dose levels studied are shown in Table 1. At the 2 lower tablet doses, although the C_{max} achieved after dosing with the tablet formulation tended to be higher than that with the capsule, when based on AUC, the BA of the 2 formulations was actually very similar. However, at the highest tablet dose (250 mg), the exposure delivered by the tablet formulation (both C_{max} and AUC) was higher than that delivered by the capsule.

Table 1: Relative bioavailability of tablet versus capsule formulation

Parameter	25mg tablet dose vs 50mg capsule dose	50mg tablet dose vs 100mg capsule dose	250mg tablet dose vs 400mg capsule dose
C_{max} ratio	1.29	1.53	2.49
95% CI	0.92-1.81	1.17-2.00	1.93-3.20
AUC ratio	1.03	0.99	1.74
95% CI	0.83-1.27	0.71-1.38	1.27-2.38

AUC, Area under the plasma concentration-time curve; CI, Confidence interval; C_{max} , Concentration maximum(plasma).

On multiple dosing, a 200mg tablet BID dose gave plasma exposure within the range of those achieved following 400mg BID capsule dose (6.88ug/ml vs 5.71 ug/ml) but the average AUC_{0-12} and C_{min} were lower (36.1ug/ml vs 43.1 ug/mL and 1.00ug/mL vs 1.86ug/mL, respectively) than achieved in a separate cohort of patients following the 400mg BID capsule dose. In addition, steady state data generated from a further cohort of patients randomised to BID dosing with both 200mg tablets and 400mg capsule dose (n=6) demonstrated that the 2 formulations could not be concluded to be bioequivalent (treatment ratio for C_{max} was 0.99 (90% CI:0.85 to 1.15) but for AUC_{0-12} was 0.79 (90% CI:0.65 to 0.94). Following multiple doses at 250, 300, 350 and 400mg BID, exposure continued to increase with dose. Please refer to the IB for further data on the tablet formulation.

The dose escalation phase of the ongoing Phase I bioavailability trial (D0810C00024) has been completed and has shown 400 mg BID to be the maximum tolerated tablet dose with frequent dose limiting toxicities being observed at higher doses. The study is now further evaluating the tolerability and clinical activity of two tablet doses - 300 mg BID and 400 mg BID. Preliminary data suggest that 400mg BID olaparib tablets is well tolerated over the first 4 weeks of treatment. In this trial the starting dose of olaparib tablets will be 400mg BID. It is envisioned that a proportion of patients will require dose reductions to 300mg BID, 200mg BID or 100mg BID respectively for cumulative toxicity over the course of several months of treatment.

4 TRIAL OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to evaluate the anti-tumour activity of olaparib in patients with advanced CRPC who have progressed following one or two chemotherapy regimens including taxane-based regimens.

4.2 Secondary Objectives

The secondary objectives are to evaluate:

- Radiological progression-free survival (rPFS)
- Time to radiological progression
- Progression free survival (PFS)
- Overall survival
- Time to PSA progression
- Duration of PSA response (decline of $\geq 50\%$)
- PSA objective response (PSA-ORR)
- The utility of CTCs as an early indication of benefit from PARPi therapy
- Further characterise the safety profile of olaparib in advanced CRPC patients

4.3 Tertiary/exploratory Objectives

- To evaluate clinical benefit as indicated by an improvement in pain measurements (BRI-SW)
- To evaluate DW-MRI imaging in selected patients and to correlate these results with PSA, CTC and radiological responses by conventional imaging

5 TRIAL ENDPOINTS

5.1 Primary Endpoints

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

- Objective response by modified RECIST (baseline lymph node size must be $\geq 2\text{cm}$ to be considered a target lesion) (Appendix E) or
- Conversion of circulating tumour cell count (CTC) from $\geq 5/7.5$ ml blood at baseline to $< 5/7.5$ ml blood nadir confirmed by at least two readings 4 weeks apart or
- PSA decline of $\geq 50\%$ (according to the PCWG2) (Appendix D)

Failure will be defined as;

- Progression by RECIST – increase in measurable lesion size (S) or new lesion AND/OR
- Progression by bone scan – see Appendix D

5.2 Secondary Endpoints

- Radiological progression-free survival (rPFS)
- Time to radiological progression
- Progression free survival (PFS)
- Overall survival
- Time to PSA progression
- Duration of PSA response (decline of $\geq 50\%$)
- PSA objective response (PSA-ORR)
- Proportion of patients with conversion of CTC count to $< 5/7.5\text{ml}$ blood nadir
- Safety and tolerability profile of olaparib in patients with metastatic CRPC

5.3 Tertiary/exploratory Endpoints

- Impact of olaparib treatment on bone metastases imaged by DW-MRI in selected patients (optional) and to correlate these results with PSA, CTC and radiological responses by conventional imaging
- Proportion of patients achieving pain improvement

6 TRIAL DESIGN

This study is divided into 2 parts; Part A & B. Part A is an efficacy screening stage for sensitive biomarkers. It is designed as an open-labelled, non-randomised two stage design both to allow the activity of olaparib in unselected advanced CRPC patients to be evaluated and to permit the development of predictive biomarkers of response to olaparib. Part B is a subsequent validation stage which will be undertaken if confirmation of activity in a biomarker defined subgroup is necessary. It is an open-labelled, single stage assessment of anti-tumour activity of olaparib in preselected patients based on putative biomarkers of HR repair deficiency previously identified in Part A. A total of up to 89 evaluable patients will be enrolled to Parts A & B.

Patients with advanced CRPC who have consented to participate in this trial will be screened and enrolled into either Part A or Part B of the study depending on which part of the study is running at the time of patient enrolment. Patients will be administered oral olaparib tablets, 400mg BID continuously until disease progression is documented and confirmed (i.e., confirmed radiographic progression) or withdrawal for another reason (see section 10.10). Paraffin embedded tumour blocks or sections from the archival tumour tissue at the time of the original diagnosis or from a biopsy / resection of metastatic disease is mandated from all subjects who enrol on the study. These samples should be obtained during the screening period after written informed consent has been obtained. All patients participating in this trial (Part A & B) will also have mandatory circulating tumour cells (CTCs), plasma and fresh tumour biopsies collected at pre-specified times during the study (Table 2). The tumour material will be analysed for biomarkers of sensitivity (response) to PARP inhibition. These tests will include *PTEN* and *ERG* expression, *ETS* gene

rearrangements and *PTEN* deletions, markers of cell cycle, DNA damage and repair including geminin expression, RAD51 and gamma H2AX foci formation, etc. Other biomarkers identified to be relevant to HR pathway from other translational research may be studied in parallel. Response to treatment with olaparib will be correlated to all the biomarkers evaluated.

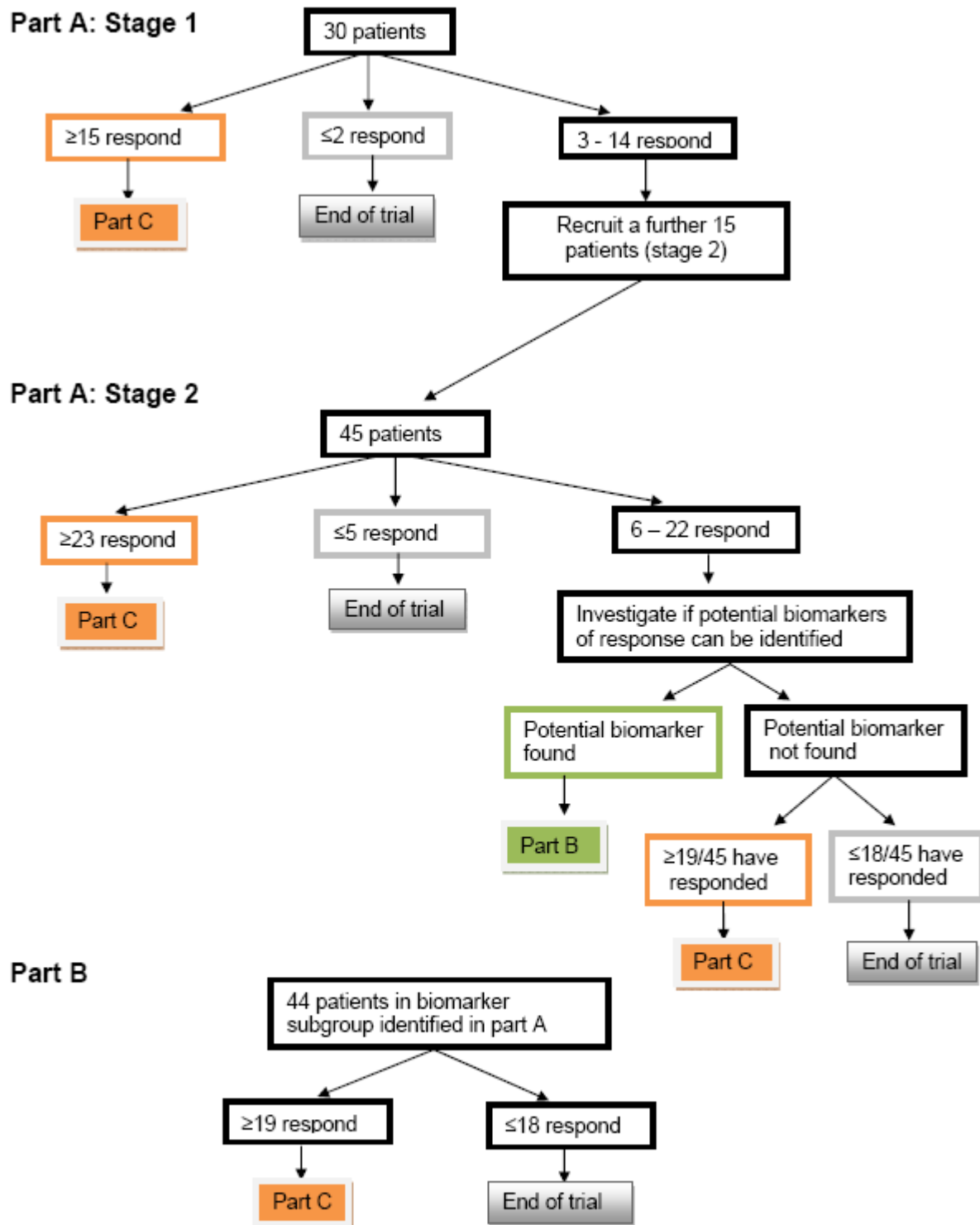
In PART A, accrual will be in unselected patients. The tumour tissue in responders versus non-responders from Part A will be evaluated to develop a molecular classifier for response to olaparib in CRPC patients that can then be utilised to select patients in Part B in the absence of evidence of a high overall response rate in PART A. Patients registered for Part B will be made aware that their tumour tissue will first be analysed for the relevant predefined biomarkers to determine their suitability for participation following consent in Part B of the study.

Disease status will be assessed at regular intervals during the course of the trial by CTC enumeration, computed tomography (CT) scan and / or on magnetic resonance imaging (MRI), diffusion-weighted MRI (DW-MRI), radionuclide bone scans and PSA. Each site should ideally designate the same reader who will evaluate the images for any one patient for the duration of the trial. Throughout the study, safety and tolerability will be assessed by the recording of adverse events; the monitoring of vital signs and physical examinations; and safety laboratory evaluations. Local laboratories will be used for the safety bloods. An independent Data Monitoring Committee (IDMC) will monitor safety data on an ongoing basis. Patient may continue on olaparib for as long as the patient is free of intolerable toxicity and is, in the opinion of the investigator, deriving clinical benefit. Patients may however elect to withdraw from the study at any point without prejudice to further treatment. Patients will have a safety follow-up visit 30 days +/-5 after their last dose of study drug for safety and end of treatment assessments.

Although outlined in the trial schema below, Part C is not currently included in this protocol but may be incorporated following completion of Parts A & B as an amendment to this protocol. PART C will be the subsequent randomised evaluation of olaparib versus an appropriate standard of care comparator to be decided at the time of initiating the amendment. Part C will only be initiated if there is sufficient evidence of antitumour activity observed either in the unselected or selected CRPC patients to warrant further evaluation of olaparib in a randomised setting. This will occur following the evaluation of safety, efficacy and biomarker analysis from Parts A and B by the Independent data Monitoring Committee (IDMC) and will involve a separate funding application and regulatory approvals. Patients in Part C may be either preselected patients based on the molecular determinants of response as identified in Parts A and B, or be unselected, depending on the response that has been seen in Parts A and B.

More details on the design of the trial can be found in the statistical considerations section.

6.1 Study Flow Chart



Part C will only be initiated if the anti-tumour activity observed in Parts A and B are sufficient to warrant a randomised study. The design of Part C will be determined following the analysis of Parts A/B.

Figure 3: Adaptive TOPARP Trial Schema

7 PATIENT SELECTION & ELIGIBILITY

Subjects with advanced progressing CRPC who have had either one or two previous lines of taxane-based chemotherapy will be invited to participate in the TOPARP study.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to safeguard the integrity of the study results.

7.1 Number of Patients

Part A: 30-45

Part B: 44

7.2 Source of Patients

Several oncology centres in the United Kingdom with extensive experience in conducting phase II/III trials have agreed to participate in this trial. Patients who have progressing castration-resistant metastatic prostate cancer will be offered participation in this trial.

7.3 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in the study:

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 taxane-based 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:
 - At least 28 days since the completion of prior flutamide treatment. Patients whose PSA did not decline in response to antiandrogens given as a second line or later intervention will only require a 14 days washout prior to Cycle 1, Day 1.
 - 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.

- 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:
 - 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 $\mu\text{g/L}$ (2 ng/ml); patients on systemic glucocorticoids for control of symptoms must have documented PSA progression by PCWG22 while on systemic glucocorticoids prior to commencing Cycle1 Day1 of treatment.
 - 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 $\geq 50\%$)
 9. Life expectancy > 12 weeks.
 10. Patient must be able to swallow a whole tablet.
 11. Patient and the patient's partner of childbearing potential, must agree to use medically accepted methods of contraception (e.g., 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 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:
 - Haemoglobin ≥ 10 g/dL independent of transfusions
 - White blood cells $> 3 \times 10^9/\text{L}$
 - Absolute neutrophil count $\geq 1.5 \times 10^9/\text{L}$
 - Platelets $\geq 100 \times 10^9/\text{L}$
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) except for patients with known Gilbert's syndrome.
 - Aspartate transaminase (AST) (SGOT) and alanine transaminase (ALT) (SGPT) ≤ 2.5 x ULN or ≤ 5 x ULN in the presence of liver metastases.
 - Serum creatinine ≤ 1.5 x 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:

$$\text{GFR} = \text{CrCl (ml/min)} = (140 - \text{age}) \times \text{wt (kg)} / (\text{serum creatinine} \times 72)$$
 - Albumin > 30 g/dl

7.4 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

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 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 have experienced a seizure or seizures within 6 months of study treatment or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in patients not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital (see Section 12.13)).
11. Patients receiving any of the following classes of inhibitors of CYP3A4 (see Section 12.13 for guidelines and wash out periods);
 - 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 investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's 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

7.5 Restrictions

1. Patients must refrain from fathering a child or donating sperm during the study and for 3 months following the last dose of olaparib. Patients of child bearing potential and their partners, who are sexually active must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after the last dose of study drug. Reliable methods of contraception should be used consistently and correctly. Acceptable methods of contraception to be used in this study include:
 - Condom with spermicide and one of the following:
 - Oral contraceptive or hormonal therapy (e.g. hormone implants)
 - Placement of an intra-uterine device
 - Acceptable non-hormonal birth control methods include:
 - Total sexual abstinence. Abstinence must be for the total duration of the study and for 3 months following the last dose of olaparib
 - Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
 - Tubal occlusion plus male condom with spermicide
 - Intrauterine Device (IUD) plus male condom and spermicide - Provided coils are copper-banded
 - Acceptable hormonal methods:
 - Etonogestrel implants (eg, Implanon, Norplan) and male condom with spermicide
 - Normal and low dose combined oral pills+male condom with spermicide
 - Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
 - Intravaginal device and male condom with spermicide (eg, EE and etonogestrel)
 - Cerazette (desogestrel) and male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.
2. No other chemotherapy or other novel agent is to be permitted during the course of the study with the exception of continued used of LHRH agonist. Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be adequately be managed with analgesics as long as the patient does not meet the criteria of disease progression or treatment discontinuation.
3. Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.
4. In vitro data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, **to ensure**

patient safety all patients must avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity (see Section 12.13) from the time they enter the screening period until 30 days after the last dose of study medication.

8 OVERVIEW OF STUDY PROCEDURES

8.1 Informed Consent

The study objectives, overall requirements, potential benefits and risk will be discussed with potentially eligible patients. Interested patients will be given a TOPARP patient information sheet. Consent must be obtained only after allowing the patient sufficient time for consideration, and the opportunity to ask any further questions. A signed, TOPARP written informed consent form must be obtained from the patient in accordance with local practice and regulations. Pre-entry tests, not performed routinely as part of standard patient management, will only be done after the TOPARP consent form has been signed and personally dated by both the patient and the Investigator. Confirmation of the patient's informed consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed form will be provided to the patient and the original retained in the investigator site file and must be available for verification by ICR-CTSU study staff or for regulatory audit/inspection at any time. Patients who consent on the TOPARP study, consent to having fresh tumour biopsies, archival tumour tissue, CTCs and plasma collected for molecular and biomarker studies.

Patients who wish to have diffusion weighted MRI (DW-MRI) scans to assess their disease during the study will be required to sign a specific DW-MRI consent form. Participation in this component of the study is entirely voluntary. Refusal to participate in the DW-MRI component of the study will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.

8.2 Registration

Once informed consent has been obtained, patients must be registered for screening by contacting the ICR CTSU:

To register a patient telephone ICR-CTSU
On: 0208 643 7150
(09.00 – 17.00 Monday to Friday)

The following information will be required when registering the patient:

- Name of cancer centre, treating hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent
- Patients initials and date of birth
- Confirmation of diagnosis

The patient will be allocated a unique registration number.

8.3 Eligibility status and trial entry

Once all screening evaluations have been completed, an eligibility checklist should be completed by the clinician/research nurse. The eligibility checklist should be completed for all patients registered.

For those patients who remain eligible, the clinician / research nurse should contact ICR-CTSU to confirm eligibility and obtain a trial number.

To confirm patient eligibility telephone ICR-CTSU

On: 0208 643 7150

(09.00 – 17.00 Monday to Friday)

The following information will be required:

- Patient's full name, hospital number, NHS number, postcode and trial registration number.
- Confirmation of the patient's eligibility status according to the eligibility checklist
- Confirmation that the evaluable disease being followed in the trial has been assessed by either CT or MRI and a bone scan within 28 days of scheduled start date of treatment
- Confirmation of consent for the trial

If the patient is confirmed as eligible for trial entry, the caller will be given the patient's unique trial identification number (Trial ID), and fax confirmation will be sent to the appropriate pharmacist to enable dispensing of the study drug.

A screening log should be completed for all registered patients who do not subsequently enter the study. This will record reasons for exclusion e.g. because screening tests identified that they were ineligible or the patient subsequently withdrew consent.

9 OVERALL STUDY ACTIVITIES

9.1 Screening Period

All patients must sign the TOPARP written informed consent before study specific screening procedures can be performed. Consent may be obtained up to 28 days prior to Cycle 1, Day 1. Patients will have a screening period of up to 28 days prior to Cycle 1 Day 1. The laboratory investigations (haematology, electrolytes, tumour markers, CTCs and testosterone level) must be performed within 14 days of starting treatment on olaparib. For details of the schedule and nature of the screening assessments, refer to Table 2 (page 56). All the screening assessments must be complete and eligibility criteria met prior to enrolment into the study. Patients who meet the eligibility and screening requirements will

return to the site for Cycle 1 Day1 visit. As part of the screening process, CTCs, a pre dose biopsy and blood samples will be collected for the predefined biomarkers of interest.

9.2 Treatment Period

All screening assessments must be completed and reviewed prior to the commencement of Cycle 1 Day 1 assessments. In the event that Screening and Cycle 1 Day 1 visits coincide, Cycle 1 Day 1 assessments do not need to be repeated. Olaparib at a dose of 400mg will be administered orally twice daily, once in the morning and once in the evening, continuously. Patients may receive continuous treatment for as long as they remain free from intolerable toxicity, and, in the investigator's opinion, are receiving clinical benefit. The patient will return on Day 8 and Day 15 of Cycle 1 and subsequently on the first day of each treatment cycle in order to evaluate safety, tolerability and dosing compliance. From Cycle 2 to end of study treatment patients' Day 1 visits will occur on a 28 day cycle with a +/- 2 day window. If the study window is utilised every effort will be made for the patient to return to schedule. Patients will have additional imaging visits up to 8 days before Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1, after every 3 cycles thereafter and treatment discontinuation. For details of the schedule and nature of the on-going assessments, refer to Table 2. The dose of olaparib may be reduced and/or a treatment delayed in patients experiencing toxicities according to the dose modification guidelines as set out in section 12.8. Safety parameters will be continuously followed-up during the duration of the trial.

9.3 End of Treatment (EOT) Visit

All patients will return for an end of treatment visit 30 +/-5 days from the time of last dose of treatment for safety and end of study treatment assessments. For details of the schedule and nature of the assessments for this end of study treatment visit, refer to Table 2 and section 11.2.5

9.4 Follow Up Visits

Following treatment completion, patients will be followed for survival every 3 months.

10 OVERALL TRIAL ASSESSMENTS

10.1 Clinical Measurements

The Investigator will ensure that all data collected in the study are provided to ICR-CTSU. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the Case Report Form (CRF) in accordance with instructions provided.

10.2 Medical History

Medical and Surgical History

Medical and surgical history, including a history of the disease being studied, other significant past and on-going conditions should be recorded. All previous radiotherapy and chemotherapy, as well as any other therapy received for prostate cancer, must be documented.

Recording of Concomitant Medications

The use of or any change in the patient's concomitant medications will be recorded when the patient visits the hospital (including a review of the patient's diary card for any self-administered medication).

Current Signs and Symptoms

Current signs and symptoms of the disease will be recorded, together with the appropriate NCI-CTC grade and causality, if appropriate.

10.3 Physical Examination

Evaluations should be performed by the same evaluator throughout the study whenever possible. A full physical examination will include the assessment of the body systems listed below and reporting if these findings were normal, abnormal or not done. A full examination will be conducted at the screening visit, cycle 1 day 1 and the end of study treatment visit. At all other times the extent of the examination beyond vital signs and weight will be conducted as clinically indicated. Height will be recorded at screening visit only. Vital signs include blood pressure, heart rate, respiratory rate, and oral or aural body temperature.

The following must be assessed and recorded:

- General appearance
- Cardiovascular
- Respiratory
- Gastrointestinal
- Genitourinary
- Central Nervous System
- Dermatological
- Musculoskeletal
- Peripheral lymph nodes
- Other

10.4 ECG Monitoring

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the Investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. An ECG assessment will be performed at screening as a baseline assessment. Subsequent ECGs will only be performed if clinically indicated.

10.5 Brief Pain Scores

The BPI-SF will be self-administered in the clinic to the patients on the first day of each treatment cycle and the results recorded in the patient's notes (Appendix I)

10.6 Blood, Tissue and Other Sampling

Blood samples for safety assessments will be done at the local institutes. Tests relating to biomarker work on CTC, plasma and tumour material will be performed primarily at The Institute of Cancer Research Cancer Biomarkers Laboratory. Samples will be collected and processed according to specified detail in the TOPARP Laboratory Manual. There may be a requirement to send some of the samples to be processed in a different laboratory. This will be done with contractual agreements in place and patient details will remain confidential.

Bone marrow or blood cytogenetic analysis may be performed according to standard haematological practice for patients with prolonged haematological toxicities as defined in Section 3.3. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to ICR-CTSU (see section 13)..

Routine clinical laboratory tests will include the following;

Table 1: List of Laboratory Tests

Local Laboratory Tests		
<p>Haematology:</p> <ul style="list-style-type: none"> • NeutrophilsHaemoglobin (Hgb) • Platelet count with differential • White blood cell (WBC) countLymphocytes <p>Coagulation Factors: Prothrombin Time (PT), Partial ThromboplastinTime (PPT), International Normalized Ratio (INR)</p>	<p>Serum Chemistry:</p> <ul style="list-style-type: none"> • Albumin (ALB) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT;SGPT) • Gamma-glutamyltransferase (GGT) • Amylase • Aspartate aminotransferase (AST;SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Chloride (Cl) • Creatinine (Cr) • Glucose • Lactate dehydrogenase (LDH) • Magnesium • Phosphate • Potassium (K) • Sodium (Na) • Total bilirubin • Total protein • Uric acid • Bicarbonate 	<p>Urinalysis dipstick for:</p> <ul style="list-style-type: none"> • Blood • Protein • Glucose • (Microscopic examination if abnormal) <p>Additional laboratory tests:</p> <ul style="list-style-type: none"> • Prostate specific antigen (PSA) • Serum testosterone • Neuron specific enolase • Chromogranins <p>In the event of protracted myelosuppression:</p> <ul style="list-style-type: none"> • Bone marrow or blood cytogenetic analysis
Central Laboratory Tests		
<ul style="list-style-type: none"> • Circulating Tumour Cells (CTCs) for enumeration & molecular characterisation • Circulating tumour DNA 	<ul style="list-style-type: none"> • Circulating tumour microRNA (miRNA) • Plasma for biomarkers 	<ul style="list-style-type: none"> • Mandatory tumour biopsy • Urine telopeptides

10.7 Efficacy Measurements

CT or MRI Scan Assessments (Modified RECIST)

Baseline contrast-enhanced CT of the chest, abdomen and pelvis should be performed for the assessment of measurable lesions. Where contrast is contraindicated then either an

MRI of the chest, abdomen and pelvis or a non-contrast CT scan can be performed if the measurable disease is easily discernable without contrast. All baseline CT will be performed during the 28-day screening window as close as possible to Cycle 1, Day 1 of treatment. The CT scans will be repeated up to 8 days before Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3rd cycle subsequently (Table 2). CT scans may be performed earlier if clinically indicated. Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed for the purposes of the study if they were performed within the correct time frame and are of sufficient quality. Subsequent, repeat imaging requires the same method of assessment to characterise each identified lesion at baseline and during follow-up. Response categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) (refer to Appendix E) will be assigned at the scheduled visits. In the case of stable disease, measurements must have met the stable disease criteria at least once after study start for a minimum interval of 12 weeks. PR or CR by RECIST must be confirmed with a repeat tumour assessment 4 weeks after the criteria for response was met.

For the purposes of analysis, overall response using Investigator measurements of target lesions, assessment of non-target lesions and new lesions collected on the CRF to derive the best overall response, and other protocol endpoints using these data. All medical images and tumour response assessments will be collected and retained on site as source data. A central image review may be performed by the sponsor if required.

Bone Scan Assessments

Bone scans will be used to assess bone lesions. Baseline bone scans will be performed during the 28 day screening window as close as possible to Cycle 1 Day 1, and up to 8 days prior to Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3rd cycle subsequently (Table 2). Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed as the baseline study if they were performed within the correct time frame and are of sufficient quality. **Bone deposits will be reported as absence or presence of new bone lesions. New lesions at the first scheduled reassessment at Week 12 must be confirmed by a second scan performed 6 or more weeks later. Disease progression by bone scan will be defined as two new bone lesions at the first 'progression' scan, confirmed by a further scan at least 6 weeks later (see section 10.9 for more details).** All medical images and tumour response assessments will be collected and archived locally. A central image review may be performed.

Diffusion weighed-MRI (DW-MRI) Scan Assessments

DW-MRI constitutes an optional component of the study. DW-MRI provides additional information regarding tumour cellularity and tumour cell death that cannot be evaluated with other imaging techniques. DW-MRI will be obtained at baseline (screening), up to 8 days prior to Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3 cycles subsequently. These results of these scans will not be utilized for the purpose of assigning disease status. Patients who wish to participate in this optional component of the study will be required to sign a separate Patient Informed Consent Form (PICF).

PSA Measurements

PSA will be assessed at baseline and routinely on day 1 of every 3rd cycle (12 weeks) by PCWG2 criteria (refer to Appendix D). Increases and decreases will be tracked in order to assess PSA responses. PSA changes from baseline to 12 weeks (either increment or decline) and maximal change in PSA will be recorded. Responses by PCWG2 criteria must be confirmed 28 days later.

Although serial PSA will be measured on this study and PSA progression documented by the PCWG2 criteria, the PSA value on its own is not considered a reliable measure of clinical benefit and does not correlate tightly with survival. PSA flares may occur early in the treatment and may therefore confound response assessment. Additionally, there is emerging data that PARP-1 is implicated in multiple other essential cellular functions separate from DNA repair including *ETS* gene-mediated transcription regulation which may have a bearing on the response assessments by PSA. PSA reading should not be applied as the sole criteria to consider treatment discontinuation. In absence of evidence of radiological or clinical evidence of disease progression, patients should continue in the study despite an increment in PSA. **Overall, therefore patients will not be taken off trial purely for rising PSA levels in the absence of worsening scans and symptoms since PARP inhibitors are likely to impact tumour growth without impacting PSA secretion.**

PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG2 criteria:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA from screening (baseline) PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- For patients with PSA declines at Week 13, the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. For patients with no PSA declines at Week 13, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented, which is confirmed by a second consecutive value four or more weeks later.

CTC Conversion Rate

CTCs will be obtained at various time points before, during and after treatment for enumeration and molecular characterisation (Table 7). CTC enumeration will be performed at The Institute of Cancer Research laboratories using the analytically valid CellSearch system (Veridex, LLC). For patients with baseline CTC counts of ≥ 5 cells/7.5 ml of blood, a conversion is defined as a nadir decline in the CTC count to < 5 cells/7.5 ml of blood. The conversion of CTC counts that are ≥ 5 to < 5 and percentage decline of $\geq 30\%$ indicative of clinical benefit and improved survival outcome will be measured (76,77,78).

A central review of bone scans and CT scans will take place. Anonymised copies of bone and CT scans should be sent to ICR-CTSU for central review on their request.

10.8 Safety Measurements

Safety parameters will be continuously assessed throughout the study prior to each cycle of treatment. These will include:

- Medical history, vital sign measurements, physical examination, and body weight
- Haematology, clinical chemistry, urinalysis
- Eastern Cooperative Oncology Group (ECOG) performance status
- Assessment of concomitant medications
- Adverse events (AEs) and serious adverse events (SAEs) including laboratory test AEs will be graded and summarised according to the NCI CTCAE version 4.02

10.9 Criteria For Discontinuation Of Study Treatment

The consensus guidelines of the PCWG2 recommend that confirmed radiographic progression is the most reliable indicator of clinical benefit in patients with CRPC. Based on this consideration, patients should be maintained on study treatment until confirmed radiographic progression or clinical progression or if the treating physician decides to initiate new systemic anti-cancer therapy. It is recommended that if the patient has PSA progression but no unequivocal clinical or radiological progression and an alternate treatment is not indicated, the investigators should maintain the patient's treatment until radiological disease progression is documented and confirmed. However, if the patient has unequivocal clinical progression without radiographic progression, these patients could be considered for other therapy at the discretion of the treating physician. In this circumstance, study treatment should be stopped and the patient advised regarding available treatment options. The intent of these criteria is to maintain study treatment for patients with PSA progression, given the absence of alternative treatment options available to participants who have failed both castration and chemotherapy and the high likelihood that some clones of prostate cancer may be benefiting in the context of radiological stability despite a PSA rise.

A patient is considered to have progressed on study if one or more of the following findings occur:

1. Progression by bone scan:

- The first bone scan with ≥ 2 new lesions compared with baseline is observed ≤ 13 weeks from cycle 1 day 1 and is confirmed by a second bone scan taken ≥ 6 weeks later showing 2 additional new lesions (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan)
- The first bone scan with ≥ 2 new lesions compared with baseline is observed > 13 weeks from cycle 1 day 1 and the new lesions are verified on the next bone scan ≥ 6 weeks later (i.e. a total of ≥ 2 new lesions compared with baseline).

2. Progression of soft tissue /visceral disease by modified RECIST:

- A patient will be determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions by modified RECIST. **Lymph nodes have to be >2 cm in size to be deemed measurable.**

3. Unequivocal evidence of clinical progression:

A patient can be taken off study at the discretion of the treating physician under the following circumstances:

- Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumour progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to grade 3 or higher felt by the investigator to indicate clinical progression
- Felt to be in the best interest of the patient to come off study due to clinical progression

4. Death from any cause.

When study treatment is discontinued due to unequivocal clinical progression, attempts should be made to determine the patient's status at the End of Treatment Visit to assess for radiographic progression, including a confirmatory bone scan, as deemed appropriate by the treating team.

10.10 Withdrawal from Study Treatment

Criteria for withdrawal of study treatment are outlined below:

1. Patient Withdraws Consent

Patients have the right to withdraw from the study at any time, without prejudice to their medical care, and are not obliged to state their reasons. If the patient withdraws consent, he should be encouraged to have a complete End of Treatment (EOT) visit and effort should be extended to clarifying the reason for the withdrawal.

Investigator may choose to withdraw a patient at any point if this is considered to be in the patient's best interest. The patient must be discontinued from the study treatment due to any of the safety reasons outlined below:

2. Sustained or Recurrent Unacceptable Side Effects:

- Any grade 3 or 4 events that have not reverted to grade 1 or the baseline (Cycle 1 Day 1) grade after a 42 days break off treatment with appropriate medical intervention. At the Investigator's discretion, patients may be considered for dose reductions [see Section 12.8 for management of toxicity & dose adjustments, providing they have not already undergone 2 dose reductions to 300 mg BID and 200 mg BID. If the grade 3 or 4 adverse events recurs at the lowest dose level (100 mg BID) then the patient must be discontinued].
- Unacceptable adverse events or any other toxicity in the investigator's opinion.
- Serious intercurrent illness or significant worsening of intercurrent illness that prevents further administration of treatment.
- A severe drug reaction or a hypersensitivity reaction to olaparib.

3. Non-compliance with Dosing or Trial Protocol Requirements

Patient is unable to adhere to study visit schedule or comply with protocol requirements despite several reminders about the requirements and efforts made to identify and resolve the aetiology of the problem may be discontinued at the discretion of the Investigator.

4. Progressive Disease

Evidence of clinically significant progressive disease as defined in section 10.9.

5. Use of Prohibited Concurrent Medication

The patient will be discontinued from the protocol treatment when prohibited drug is administered. Supportive care medications are permitted with their use following institutional guidelines.

6. Other Reasons

Additionally, patients may be discontinued from study treatment for any of the following reasons:

- Patient lost to follow-up
- If in the opinion of the Investigator, a change of therapy would be in the best interest of the patient
- Major protocol violation
- Incorrectly enrolled patients, i.e., the patient does not meet the required inclusion/exclusion criteria for the study

Attempts should be made to contact any patient failing to return for a scheduled visit/follow up, in order to ensure that the reason for not returning is not an adverse event. Likewise attempts should be made to establish whether any patient declaring a desire to discontinue from the study e.g. for personal reasons, is in reality due to an adverse event (AE). If the olaparib therapy is prematurely discontinued, the primary reason for discontinuation must

be recorded in the appropriate section of the CRF. Patients will be required to attend an end of treatment visit at least 30 +/- 5 days after discontinuing study medication for collection and/or completion of AE information. All new events occurring during this 30-day period must be recorded (if SAEs they must be reported to the ICR-CTSU within 24 hours) and followed-up to resolution, unless in the opinion of the Investigator, the condition is unlikely to resolve due to the patients' underlying disease. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the Investigator assesses as possibly related to the study medication should also be reported as an AE. The patient should return all study medication following cessation of the study drug.

In the unlikely event that a patient withdraws consent for further follow-up data to be collected, the appropriate form in the CRF should be completed and returned to ICR-CTSU. Clarification should be sought to ensure that the patient is not simply withdrawing from study drug. In the extremely unlikely event that the patient wishes to have their data removed from the trial completely (the implications of this should be discussed with the patient to ensure that this is their intent), this should be indicated as such on the form.

10.11 Patient Replacement Policy

An evaluable patient is defined as a patient who:

- Meets all of the inclusion and exclusion criteria specified in Sections 7.3 and 7.4 within the specified time frame;
- Has adequate histological tissue for the biomarker analysis.
- Completes twelve weeks of treatment with olaparib or experiences an event defined as treatment failure within twelve weeks.

Patients who prematurely withdraw from the study for reasons other than treatment failure may be replaced. Patients who become non-evaluable e.g. by ceasing to take LHRH agonists, may also be replaced. Replacement of ineligible and non-evaluable patients will be dependent on authorisation by the Independent Data Monitoring Committee (IDMC)

Note: Rising PSA or worsening bone scans in the first 12 weeks is NOT treatment failure and may reflect a flare response.

11 TRIAL ASSESSMENTS BY VISIT

A case report form (CRF) will be provided by ICR-CTSU for each patient eligible for the trial. The relevant forms should be completed at each hospital visit and sent to the ICR CTSU in a timely manner.

11.1 Baseline Assessments

11.1.1 Screening

Screening activities that involve imaging and collection of archival and fresh tumour tissue will be conducted within a 28-day window prior to commencing Cycle 1 Day 1. All other screening activities/procedures outlined below will be conducted during the screening period over 14-days prior to Cycle 1 Day 1.

- Obtain archival tissue for analysis of biomarkers (Days -28 to Day 1) Please refer to section 15, for further details of specimens to be collected.
- Obtain mandatory fresh tumour biopsy (Days -28 to Day 1). Please refer to section 15, for further details of specimens to be collected.
- Medical history including details of the following:
 - All co-morbidities
 - Oncology history / family history of cancers
 - Prior prostate cancer history including extent of disease (stage), Gleason score at diagnosis, PSA levels
 - Previous hormonal, cytotoxic, and experimental treatments with start and stop dates
- Demographics
- Listing of current baseline signs and symptoms with associated NCI Common Terminology Criteria for Adverse Events grading (0-4)
- Physical examination
- Weight, and height
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG Performance Status
- 12 lead ECG
- Laboratory tests:
 - FBC: WBC with differential count, RBC, haemoglobin, hematocrit, platelets.
 - Coagulation studies (PT/PPT, INR)
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, uric acid, and magnesium
 - Urinalysis: routine dipstick. Only if the dipstick is abnormal will the urine be sent for analysis
 - PSA: If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE
 - Serum testosterone
- Baseline tumour assessment
 - CT and / or other imaging procedures as clinically indicated
 - Bone Scan
 - DW-MRI (optional)

- Pain (BFI-SF) and Analgesic Usage Score
- Concomitant medications listing
 - Obtain a complete list of all prescription and nonprescription (over the counter) medications currently taken including pain medications. This also includes any nutritional supplements and/or herbal preparations.
- Assessments of signs and symptoms
- Biomarkers
 - Circulating Tumour Cell (CTC) blood collection for enumeration and molecular characterisation
 - Circulating Plasma DNA and RNA studies
 - PAXgene mirRNA studies
 - Urine markers of bone turnover and RNA
 - Serum Proteomic studies
 - Plasma and urine metabonomic studies

11.1.2 Cycle 1 Day 1

Patients who are eligible after screening and who accept to be entered into the study should be entered within 28 days of informed consent. All the screening assessments should have been completed and screenings results reviewed prior to trial entry and the commencement of Cycle 1.

The following procedures should be carried out **prior to dosing of study treatment**:

- Update listing of current baseline signs and symptoms with associated NCI Common Terminology Criteria for Adverse Events grading (0-4)
- Updated oncology history with any events that may have transpired since screening
- Physical examination
 - Full examination
 - Vital signs including blood pressure, heart rate, respiratory rate, oral body temperature
 - Height and weight
- Assessment of ECOG Performance Status
- Laboratory Tests:
 - FBC: WBC, RBC, haemoglobin, haematocrit, platelets with differential count.
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, uric acid.
 - Urinalysis: routine dipstick. Only if the dipstick is abnormal will the urine be sent for analysis.
 - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
- Pain (BFI-SF) and Analgesic Usage Score
- Concomitant medications listing
 - Update listing of all prescriptive and non-prescriptive (over the counter)

medications taken since screening. This also includes any nutritional supplements and/or herbal preparations

- Assessment of adverse events
- Biomarkers
 - Circulating Tumour Cell (CTC)
 - Circulating plasma DNA and RNA studies
 - PAXgene miRNA studies
 - Urine markers of bone turnover (telopeptides) and RNA
 - Serum proteomic studies
 - Plasma and urine metabolomic studies

11.2 On-treatment Assessments

11.2.1 Cycle 1 Day 8 Visit

The following assessments should be carried out on Day 8:

- Brief history and physical examination as clinically indicated
- Vital signs including blood pressure, heart rate, respiratory rate, oral body temperature
- Assessment of ECOG Performance Status
- Laboratory Tests:
 - Full blood count including WBC, haemoglobin, platelets
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, uric acid, magnesium
- Concomitant Medications listing:
 - Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations
- Adverse events will be monitored throughout the study. At each post-baseline visit, the investigator will begin by querying for adverse events by asking each patient a general, non-directed question such as 'How have you been feeling since the last visit?' Directed questioning and examination will then be done as appropriate.
- Dosing compliance check
- Obtain post treatment mandatory fresh tumour tissue biopsy (Cycle 1 Days 8 to Day 28)
- Biomarkers
 - Circulating Tumour Cells (CTC)
 - Plasma and urine for metabolomic studies

11.2.2 Cycle 1 Day 15 Visit

- Biomarkers
 - Circulating Tumour Cells (CTC)

11.2.3 Day 1 of Cycles 2, 3, 5, 6, 8, 9, 11, and 12

(Continue every cycle beyond Cycle 12)

The following assessments should be carried out at the indicated time point:

- Brief history and physical examination as clinically
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Weight
- Assessment of ECOG Performance Status
- Concomitant Medications listing
 - Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations.
- AE evaluation and recording at each post-baseline visit
- PSA measurements will be conducted every 12 weeks. PSA results will be assessed according to PCWG2 criteria
- Dosing compliance check and a count of study medication will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not 100% in the absence of toxicity, patient should be re-instructed regarding proper dosing procedures
- Pain (BFI-SF) and Analgesic Usage Score (each cycle)
- Laboratory Tests:
 - FBC: WBC, RBC, haemoglobin, haematocrit, platelets with differential count
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, LDH, uric acid, magnesium
- Biomarkers
 - CTC collection (Cycles 2, 3, 4, 7, every 3rd cycle thereafter and at treatment discontinuation/EOT)
 - Plasma for DNA, RNA studies (Cycles 2, 3, 5 and at treatment discontinuation/EOT)
 - Paxgene miRNA studies (cycle 3, 5 and at treatment discontinuation/ EOT)
 - Urine and plasma metabolomic (cycles 2, 3 ,6 and at treatment discontinuation/EOT)
 - Urine markers of bone turnover and RNA (cycle 3, cycle 6 and at treatment discontinuation/ EOT)

11.2.4 Cycles 4, 7, and 10 and Treatment Discontinuation (continue every 3rd cycle beyond Cycle 10)

In preparation for the study visit, the following assessments should be conducted up to 8 days prior to the indicated visit. Results should be available for review at the Cycle 4, 7, or 10 Day-1 visit and every 3rd cycle beyond Cycle 10.

- CT Scan
- Bone Scan
- DW-MRI (optional)
- Other imaging procedures should be conducted as clinically indicated

At the study visit the following assessments should be conducted:

- Brief history and physical examination as clinically indicated
- Vital signs including blood pressure, heart rate, respiratory rate and oral body temperature.
- Weight
- Assessment of ECOG Performance Status
- Laboratory Tests
 - FBC: WBC, RBC, haemoglobin, platelets with differential count, chemistry with electrolytes: sodium, potassium, chloride, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, glucose, LDH, uric acid, magnesium, random glucose.
 - PSA (every 12 weeks): If patient undergoes a DRE, then PSA must be sampled prior to the DRE
- Concomitant medications listing
- AE evaluation and recording
- Dosing compliance check
- Pain (BFI-SF) and Analgesic Usage Score (each cycle)
- Review of imaging results (CT and bone scan) should be conducted and disease response /progression ascribed at the actual study visit (Cycle 4, 7, or 10 Day 1) unless otherwise indicated.
- Tumour biopsy (this end of study treatment biopsy is optional and can be collected at any point from treatment discontinuation up to the end of treatment visit).
- Biomarkers
 - CTC collection (Cycles 2, 3, 4, 7, every 3rd cycle thereafter and at treatment discontinuation/EOT)
 - Plasma for DNA, RNA studies (Cycles 2, 3, 5 and at treatment discontinuation/EOT)
 - Paxgene mirRNA studies (cycle 3, 5 and at treatment discontinuation/EOT)
 - Urine and plasma metabolomic (cycles 2, 3, 6 and at treatment

- discontinuation/EOT)
- Urine markers of bone turnover and RNA (cycles 3, 6 and at treatment discontinuation/EOT)
- Serum proteomic studies (at treatment discontinuation/EOT)

11.2.5 End of Treatment (EOT) Visit

Patients should return for an EOT visit 30 days +/- 5 following the patient's last dose of drug. The following assessments should be carried out at the EOT visit:

- Physical examination and weight
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature.
- Assessment of ECOG Performance Status
- 12-lead ECG is not mandated but should be done if clinically indicated
- Laboratory tests:
 - FBC: WBC, haemoglobin, platelets with differential count
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, LDH, uric acid, magnesium.
 - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
 - Disease Progression Assessment Review of imaging (CT, Bone scan, DW-MRI) results assessment according to modified RECIST and PCWG22 criteria.
 - Review of PSA results conducted over the course of the study and PSA progression assessment according to PCWG2 criteria
- Concomitant medications listing: update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations.
- Adverse events
 - AE follow-up to determine if any new or ongoing drug-related AE or any SAE regardless of relationship to study drug exists is required for 30 days post last dose or until patient receives anticancer therapy, whichever comes first
- Final dosing compliance check if not performed when treatment discontinued.
- Pain (BFI-SF) and Analgesic Usage Score
- Biomarkers
 - Circulating CTC collection (if not obtained at treatment discontinuation)
 - Circulating plasma for DNA, RNA studies (if not obtained at treatment discontinuation)
 - Paxgene mirRNA studies (if not obtained at treatment discontinuation)
 - Urine and plasma metabolomic studies (if not obtained at treatment discontinuation)
 - Urine markers of bone turnover and RNA (if not obtained at treatment

- discontinuation)
- Serum proteomic studies (if not obtained at treatment discontinuation)

11.2.6 3 monthly follow up (3 monthly from EOT))

Following treatment completion, patients will be followed for survival. Additional information as to whether they have started any platinum-based chemotherapy, mitoxantrone or another PARP inhibitor will be obtained where feasible. Follow-up data may be collected by a telephone interview.

11.3 Unscheduled Visits

Unscheduled visits and procedures may be conducted at the investigator's discretion for the safety follow-up of the patient. Such visits and procedures must be fully recorded in source documents regarding the purpose and outcome of the visit/assessment. Clinically significant laboratory results from unscheduled visits should be documented in the CRF.

11.4 Early Discontinuation

Patients will be advised in the written informed consent form that they have the right to withdraw from study drug treatment at any time without prejudice, or may be withdrawn at any time at the discretion of the investigator or the sponsor. Notification of early patient discontinuation from the study and the reason for discontinuation will be made on the protocol deviation form provided. Patients removed from therapy for any reason should continue to be followed for the collection of safety data as outlined in the EOT visit procedures. For patients who refuse or are unable to attend further clinic study visits, telephone contact should be attempted to follow up for adverse events 30 days \pm 5 days after the last dose of study drug. All serious adverse events will be followed until resolution, until the event has stabilised and/or become chronic, until it has been determined that the event was caused by aetiology other than the study drug, or through 30 days, whichever comes first. Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete study-related assessments and retrieve any outstanding data and study drug. Such efforts should be documented in the source documents.

Table 2: Schedule of Procedures and Clinic Visits

Procedures & Assessments	Screening		Cycle 1	Cycle 1	Cycle 1	Cycle 2, 3, 5, 6, 8, 9, 11, 12	Cycle 4, 7,10, every 3 rd cycle	Cycle 4, 7 ,10, and every 3 rd cycle	End of Treatment (EOT) Visit	Follow Up
	Day -28 to Day -1	Day -14 to Day -1	Day 1	Day 8	Day 15	Day 1	Up to 8 days before	Day 1	Day 30 after last dose of drug	3 monthly from EOT
Informed Consent ¹	X									
Medical History ²		X								
Obtain Archival Tissue ³	X									
Tumour Biopsy ⁴	X			X(8± 21 days)					X (optional)	
Assessment of Symptoms ⁵		X	X	X		X		X	X	
Dosing compliance ⁵				X		X(every cycle)		X		
Concomitant medication ⁵		X	X	X		X		X	X	
Adverse events ⁵			X	X		X		X	X	
Physical Examination & Vitals ⁶		X	X		X	X		X	X	
Complete Pain Questionnaire ⁷		X	X			X(every cycle)		X(every cycle)	X	
12 Lead ECG ⁸		X								
Safety Bloods ⁹		X	X	X		X		X	X	
Testosterone Level ¹⁰		X								
PSA Levels ¹¹		X	X					X	X	
Neuron specific enolase/chromogranins ¹²		X								
Imaging Assessments										
Bone Scan ¹²	X						X			
DW-MRI (optional) ¹⁴	X						X			
CT Scan ¹⁵	X						X			
Disease Progression Assessment ¹⁶	X							X	X	
Survival & further treatment										X
Blood and Urine Biomarker Tests										
Plasma DNA & RNA ¹⁷		X	X			X (C2,3,5)			X	
Circulating Tumour Cells ¹⁸		X	X	X	X	X (C2, 3)		X	X	
Blood miRNA ¹⁹		X	X			X (C3,5)			X	
Plasma Proteomics ²¹⁰		X	X						X	
Plasma and urine Metabolomic ²¹		X	X			X (C2,3,6)			X	
Markers of Bone Turnover and RNA ²²	X		X			X(C3,6)			X	

Procedures and Clinic Visits

1. Written informed consent must be obtained within 28 days period prior to Cycle 1 Day 1.
2. Medical history at screening will detail demographic, family history, co-morbidities, prior treatments for prostate cancer and baseline adverse events.
3. Archival tumour tissue will be obtained for molecular characterisation. Patients who do not have archival tumour tissue will be required to have a repeat tumour biopsy in order to obtain the required tumour tissue for molecular characterisation.
4. Fresh tumour biopsies are a mandatory component of this study and will be obtained prior to commencing treatment (during the screening period) and post treatment (at any point from Day 8 to Day 28 of Cycle 1). The third biopsy at the time of treatment discontinuation is optional.
5. At each clinic review, symptoms, concomitant medication, treatment compliance and adverse events will be assessed. Adverse events will be assigned a grade according to the CTCAE version 4.02 and causality. Adverse Event follow-up is required for 30 +/-5 days post last dose of treatment to determine if any new or on-going drug related AE or any SAE regardless of relationship to drug persists.
6. Includes physical examination, blood pressure, heart rate, respiratory rate, oral body temperature, and weight. Height will only be measured at the screening visit. A full physical examination will be performed at screening, Cycle 1 Day 1 and at the EOT visit. At all other clinic reviews physical examinations will be performed as clinically indicated.
7. A Brief Pain Inventory Questionnaire will be given to the patient to fill in at screening and at the beginning of each cycle. The Brief Pain Inventory Score will be annotated in the patients CRF.
8. ECG will only be performed at the screening visit. ECGs should be obtained with the subject in the supine resting position for several minutes. Abnormal ECG related to electrolyte abnormalities should be repeated following the correction of the electrolyte abnormalities. ECGs will only be repeated beyond screening if clinically indicated.
9. A full array of safety bloods including the full blood count, blood chemistry, liver function test, clotting profile, glucose, amylase, etc. will be obtained and checked at the beginning of each cycle of treatment.
10. Serum testosterone level will be checked during the screening period to ensure a systemically castrate state [testosterone levels of < 50 ng/dL (< 2.0 nM)]. Testing for serum testosterone, PSA and routine safety bloods will be performed at the local site laboratory.
11. PSA testing will be done at screening and every 12 weeks while on treatment. PSA responses by PCWG2 criteria will need to be confirmed 4 or more weeks later.
12. Neuron specific enolase and chromogranins A and B to be performed in patients with baseline PSA<10.
13. A bone scan will be obtained at baseline and after every 3rd cycle of treatment. New bone deposits will need to be confirmed with a repeat bone scan 6 or more weeks later.
14. DW-MRI is optional and will be performed at baseline (screening) and every 12 weeks thereafter.
15. CT scan will be obtained at baseline and after every 3 cycles of treatment. If a status of partial or complete response is made, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.
16. Disease progress assessment will be made after every 3rd cycle of treatment at the clinic visits.
17. Serum plasma for circulating plasma DNA and RNA will be collected in BD Vacutainer® CPT™ tubes (3x10mls) at screening, C1D1, C2,D1, C3,D1, C5D1 and at either termination of treatment or EOT.
18. Blood for CTC analysis should be collected at the indicated time points in 2 Cell Save™ tubes (10mL each, Veridex, PA). Patients being enrolled at Royal Marsden Hospital NHS Trusts will have an additional 1 CTC blood samples (i.e. in total 3 CTC blood samples) collected at screening and Cycle 1 Day 1 and subsequently 2 tubes at all other time points.
19. Blood samples for whole blood miRNA analysis will be collected in a 2.5ml PAXgene Blood RNA Tube at screening, Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1 and at either termination of treatment or EOT visit.
20. Blood samples (1x10mls) will be collected for PTEN proteomics profiling at screening and Cycle 1 Day1.
21. Urine and plasma metabolomic profiles will be evaluated both at baseline and during treatment. These blood samples will be collected in a 6ml BD vacutainer with heparin.
22. A 24 hour urine sample will be obtained at screening, C1D1, C3D1, C6D1 and at study termination or EOT to assess markers of bone turnover such as telopeptides..

12 TRIAL TREATMENT

12.1 Drug Manufacturer

Olaparib tablets will be manufactured and provided free of charge by AstraZeneca to participating centres. AstraZeneca will manufacture to Good Manufacturing Practice (GMP) and UK Legislation.

12.2 Presentation / Formulation of Olaparib

Olaparib is presented for oral administration as a green, oval bi-convex film-coated tablet containing 100 mg of drug substance.

12.3 Drug, Dose and Schedule

The dose of 400 mg olaparib, twice daily orally, continuous dosing has been selected for this protocol based on the pharmacokinetic (PK), pharmacodynamic (PD) and clinical efficacy data from the Phase I-II studies including an ongoing bioavailability study (10, 11, 49, 50, 61, 62). The olaparib dose should NOT be adjusted according to the patient's body weight, even for very heavy or light patients. Patients will be given sufficient supplies for 1 cycle (28 days+2) of treatment.

12.4 Instructions for Administration of Olaparib

Patients should swallow the olaparib tablets whole with a glass of water in the morning and evening at the same times each day to ensure a dose interval of approximately 12 hours. Olaparib must be administered no sooner than 1 hour after food and the patient should then refrain from eating for a further 2 hours post dose to avoid the potential effect of food on drug absorption. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. If vomiting occurs shortly after the olaparib is swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the trial miss a scheduled dose for whatever reason (e.g. as a result of forgetting to take the dose of olaparib), he will be allowed to take the scheduled dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

12.5 Olaparib Treatment Compliance

A member of the Investigative site's study team will query the patient for treatment compliance at day 1 of each new cycle of treatment. All patients must return their bottle of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Compliance will be assessed by capsule count and questioning by the study nurse and the information will be recorded.

12.6 Duration of Therapy

Patients may continue with olaparib treatment as long as they remain free from intolerable toxicity, in the Investigator's opinion, are receiving clinical benefit and do not meet any discontinuation criteria (see Section 10.9 for discontinuation criteria).

12.7 Supportive Care Guidelines

Based upon experience from Phase I and II studies, olaparib is generally well tolerated. The safety concerns are primarily related to the risk of myelosuppression. Supportive care should be provided therapeutically and prophylactically as deemed necessary by the treating physician including but not limited to the items outlined below:

Gastrointestinal symptoms

Prophylactic anti-emetics and/or anti-diarrhoeals will not routinely be given. Should a patient develop nausea, vomiting and/or diarrhoea that, in the Investigator's opinion, is considered to be related to olaparib, then appropriate prophylactic treatment may be initiated. Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

Myelosuppression

Routine prophylaxis with granulocyte colony-stimulating factor (G-CSF)/granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin is not recommended. Nevertheless, use is permitted at the Investigator's discretion and according to local hospital guidelines. The occurrence of leukopenia and/or anaemia should be managed as deemed appropriate by the investigator. The use of growth factors must be discontinued once the AE has recovered to CTCAE grade 1 or better. They may be resumed, if necessary, if leukopenia/anaemia develops again and discontinued once it recovers. The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the CRF. Checking haematinics levels (Iron, B12 and folate) and providing supplementation if these are found to be low is advocated. Transfusions may be given as clinically indicated for the treatment of anaemia and thrombocytopenia.

Symptoms Related to Castration

Treatment with androgens, estrogens and progestin to control hot flashes is not allowed. Antidepressants that do not interfere with P450 enzyme function are permitted for the management of hot flashes. Long-term androgen deprivation may lead to metabolic diseases, such as glucose intolerance, hypercholesterolemia, and osteoporosis, appropriate medication may be prescribed to manage these conditions. All such AEs need to be recorded.

12.8 Guidelines for Management of Toxicity and Dose- Modification

Based on Phase I and Phase II studies, olaparib is generally well tolerated. Safety concerns are mainly related to the possibility of myelosuppression.

Any toxicity observed during the course of the study may be managed by a dose interruption if deemed appropriate by the Investigator. Treatment must be interrupted if any clinically significant NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of olaparib.

Repeat dose interruptions are allowed as required, for a maximum of 42 days on each occasion. Olaparib must be interrupted until the patient recovers completely or the toxicity reverts to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.02) grade 1 or less. When the toxicity is appropriately resolved, the patient can resume treatment with olaparib with a dose reduction according to Table 3 if a treatment break of ≥ 14 days was required for the resolution of the toxicity. If the event recurs with the same severity following olaparib re-challenge, treatment should be interrupted again, and on resolution, a further dose reduction made. A maximum of 3 dose reductions will be allowed. Regular 7-day drug holidays will also be permitted if myelosuppression is an issue at these doses.

If, on re-starting treatment following 3 dose reductions, the event continues to occur at the same severity, treatment should be discontinued and the patient withdrawn from study. If the toxicity has not resolved to at least grade 1 during the maximum 42-day period, and/or the patient has already undergone a maximum of 3 dose reductions already, the patient must permanently discontinue treatment with olaparib. Once the dose of olaparib has been reduced under no account should it be re-escalated.

The dose of olaparib should not be reduced for grade 3-4 gastrointestinal adverse events that have not been adequately managed with appropriate prophylactic measures. In all cases where the olaparib dose has been interrupted or the patient discontinued due to unusual or unusually severe toxicity considered related to olaparib, the Investigator must contact the Chief Investigator and CTSU trial management team. All dose modifications and interruptions (including any missed doses), and the reasons for the modifications/interruptions are to be recorded in the CRF.

Olaparib should be temporarily withheld in the event of:

- Grade 4 neutropenia
- Grade 2-4 neutropenia with infection
- Platelet count lower than $50 \times 10^9/L$
- Non-haematological toxicity grade 3 or greater, except nausea, vomiting or diarrhoea and fatigue associated with suboptimal pre-medication and/or management OR transient and clinically insignificant biochemical blood results.
- Aspartate transaminase (AST) or alanine transaminase (ALT) elevations grade 3 or higher for more than 7 days.
- New or worsening pulmonary symptoms or radiological abnormality occurs which are suggestive of pneumonitis

- Any other toxicity that, in the view of the principal investigator and the medical monitor, represents a clinically significant hazard to the patient until resolution of toxicity to no more than grade 1.

Standard Dose	Olaparib Dose
First dose reduction due to NCI-CTC grade 3 or 4 treatment-related Serious Adverse Events / Adverse Events (excluding inadequately managed gastrointestinal symptoms)	300 mg BID
Recurrent episode of NCI-CTC grade 3 or 4 event despite one previous dose reduction (excluding inadequately managed gastrointestinal symptoms)	200 mg BID
Recurrent episode of NCI-CTC grade 3 or 4 event despite two previous dose reductions(excluding inadequately managed gastrointestinal symptoms)	100mg BID

Table 3: Summary Guidelines for Dose Reductions

Management of prolonged haematological toxicities including anaemia, neutropenia or thrombocytopenia whilst on study treatment

If any study treatment is interrupted/ delayed because of one or more of the following:

- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 neutropenia
- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 thrombocytopenia
- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 anaemia and or development of blood transfusion dependence

Weekly blood counts should be performed during the study treatment interruption/delay. If the levels have still not recovered to CTC Grade ≤ 1 after 42 days of dose interruption, the patient should be referred to a haematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Bone Marrow or blood cytogenetic analysis:

If a bone marrow analysis is carried out to evaluate cytopenia it should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Development of myelodysplastic syndrome should be reported as an SAE and full reports must be provided.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Chief Investigator and CTSU trial management team. All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded.

12.9 Packaging and Labelling

AstraZeneca have employed Fisher Clinical Services to coordinate IMP packaging, labelling and distribution for this trial. Olaparib will be supplied in High Density Polyethylene containers containing desiccant. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence. Olaparib will be provided to each site in labelled bottles. Each bottle will have a label permanently affixed to the outside and will be labelled in accordance with Good Manufacturing Practice and local regulations, stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. Labels will refer to Olaparib as AZD2281 and will include blank lines for quantity of tablets to be taken, patient trial ID and date of dispensing.

12.10 Drug Storage

Drug Storage by Pharmacy

All study medication must be kept in a secure place under appropriate storage conditions (at temperatures less than 30°C and protected from light). Study medication should not be stored under refrigerated conditions. Additional information is provided in the olaparib Investigator's Brochure. Any deviations from the recommended storage conditions should be immediately reported to the sponsor and the use of olaparib interrupted until authorisation for its continued use has been given by AstraZeneca and the sponsor.

Storage Requirements for the Patient

Olaparib must be stored in the bottle with the cap tightly on at room temperature. Study medication should not be refrigerated. Patients should be advised to keep all medication out of the sight and reach of young children.

12.11 Distribution of Drugs to Site

No drug will be distributed to participating centres unless ICR-CTSU is satisfied that the required approvals, agreements and initiation procedures are complete.

Participating pharmacy departments should contact Fisher Clinical Services via the ICR-CTSU trial management team to request drug supplies following patient registration.

Records must be kept for all deliveries and a copy of the order / delivery note placed in the Site Pharmacy File and kept within the pharmacy department as in routine practice. At the end of the trial, it must be possible to reconcile supply and usage of all stock. Account must be given to any discrepancies and certificates of delivery and return must be signed.

12.12 Pharmacy Responsibilities and Drug Accountability

Labelling:

Labelling will be the responsibility of Fisher Clinical Services and will be compliant with Annex 13 of the Good Manufacturing Guidelines (GMP) and all applicable local regulatory requirement. Each hospital pharmacist must also insert the name of the Principal Investigator (PI) or hospital specific code by which the PI can be identified, together with the Trial ID and patient's name,.

The local pharmacy department must designate a responsible person for ensuring that:

- The study drug is handled and stored safely and properly
- The study drug is labelled for each patient in accordance with Annex 13 of the EU Good Manufacturing Practice (GMP) Guidelines
- The study drug is dispensed only to trial patients and in accordance with the protocol and under the guidelines of the site's dispensing standard operating procedure
- Full accountability is maintained for the study drug
- Patients should be instructed to return unused olaparib, preferably in their original packs. Olaparib which has been dispensed to a patient and returned unused must not be re dispensed to a different patient
- There is a sufficient supply of study drug for patients' continued treatment, and in a timely manner, contact ICR-CTSU for re-supply of stock
- Study drug expiry dates are monitored and are used in order of expiry date order i.e. earliest expiry first
- All unused drugs will be accounted for and retained until advised otherwise. Unused and returned study drug may be destroyed locally in accordance with hospital protocol and following written instructions from the sponsor

Patient cards

Small wallet sized cards will be produced by ICR-CTSU on request by the participating centre. Each card will state:

- the name of the participating centre
- that the patient is participating in the TOPARP trial
- that the patient is taking olaparib

12.13 Concurrent Medications

The concurrent administration of other anticancer therapies, including cytotoxic, hormonal (except LHRH analogues) or immunotherapy, is prohibited during study treatment. The use of any natural/herbal products or other “folk remedies” should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded.

Olaparib is an investigational drug for which no data on *in vivo* interactions are currently available. Based on *in vitro* data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. *In vitro* data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib. Whilst this is not an exhaustive list of inhibitors, it covers the known potent inhibitors which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfonavir

For patients taking any of the above, the required wash-out periods prior to starting olaparib is one week.

In addition, to avoid potential reductions in exposure due to drug interactions, the exclusion of the following P450 inducers is recommended:

- Phenytoin, rifampicin, rifapentin, reifabutin, carbamazepine and phenobarbitone, nevirapine, modafinil and St John’s Wort (*Hypericum perforatum*)
- For patients taking any of the above, the required wash-out periods prior to commencing olaparib are:
- Phenobarbitone - 5 weeks; any of the others - 3 weeks.

If use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient’s safety and welfare, the Investigator must contact the ICR-CTSU and a decision to

allow the patient to be enrolled in the study will be made on a case-by-case basis by the Chief Investigator.

If at any time an investigator suspects a drug-drug interaction due to olaparib, an AE report should be completed and the study sponsor informed.

Permitted Concomitant Therapy

- Leuteinizing hormone-releasing hormone (LHRH) agonists to maintain a testosterone level <50g/dL should be administered in patients who have not undergone an orchidectomy.
- Conventional multi-vitamins and minerals.
- Stable chronic non-immunosuppressive systemic doses of corticosteroids up to a dose of prednisolone 5mg BID or equivalent so long as the treatment was initiated prior to commencing the trial medication with evidence of progression on the dose of steroids. Higher doses of steroids are permitted if clinically indicated for acute medical conditions.
- Initiating bisphosphonate therapy or adjusting bisphosphonate dose/regimen within 30 days prior to Cycle 1 Day 1 is prohibited. Patients on a stable bisphosphonate regimen are eligible and may continue.
- Anticoagulant Therapy: Patients who are taking warfarin may participate in this trial however, it is recommended that prothrombin time (International Normalised Ratio [INR] and activated partial thromboplastin time [APTT]) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted and is preferable given the potential for myelosuppression.
- **Palliative radiotherapy:** may be used for treatment of pain at the site of bony metastases that were present at baseline, providing the Investigator does not feel that this is an indication for the patient to come off treatment due to disease progression. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the CRF.

Therapy considered necessary for the subject's welfare and which is believed not to interfere with the study medication may be given at the discretion of the investigator. If concurrent medications may have an effect on study outcomes, a statement to the effect that these medications should be administered in dosages that remain constant throughout the course of the trial should be included. All medications (prescriptions or over-the-counter medications), the reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records.

13 PHARMACOVIGILANCE

13.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a study drug, whether or not considered related to the study drug.

Adverse Reaction (AR): all untoward and unintended responses to the study drug related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions i.e. an AR is possibly, probably or definitely related to the study drug. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR): Any untoward medical occurrence or effect which occurs from screening until 30 days after the last dose of study drug:

- **results in death:** the patient's death is suspected as being a direct outcome of the AE.
- **is life-threatening:** refers to an event in which the subject was at risk of death at the time of the event. It also refers to an event that would result in death with the continued use of the product; it does not refer to an event which hypothetically might have caused death if it were more severe.
- **requires hospitalisation, or prolongation of existing inpatient hospitalisation:** admission to hospital overnight or prolongation of a stay in hospital was necessary as a result of the AE..
- **results in persistent or significant disability or incapacity:** the AE results in a significant or persistent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- **results in a congenital anomaly or birth defect**

Hospitalisation meeting the definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Inpatient admission does not include: rehabilitation facilities, hospice facilities, skilled nursing facilities, nursing homes, routine emergency room admissions, same day surgeries (as outpatient/same day/ambulatory procedures), or social admission (e.g., subject has no place to sleep). Outpatient treatment in an emergency room is not itself an SAE, although the reasons for it may be. Hospital admissions/surgical procedures planned for a pre-existing condition before a patient is randomised to the study are not considered SAEs, unless the illness/disease deteriorates in an unexpected way during the study

Medical judgement should be exercised in deciding whether other AE/ARs are serious. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious

N.B. progressive disease and death due to disease are not considered SAEs but should be reported on the relevant forms.

Suspected Unexpected Serious Adverse Reaction (SUSAR): Any serious adverse event with a suspected relationship to study drug that is not listed on the Investigator Brochure (IB) and in the opinion of the Chief Investigator, is unexpected.

13.2 Clinical & Laboratory Adverse Events

AEs Based on Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

AEs Based on Examinations & Laboratory Tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfil any of the SAE criteria or are the reason for stopping treatment with the investigational product. If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator should use the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value).

The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms.
- Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting as an AE).
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy.
- Test result leads to any of the outcomes included in the definition of a SAE.
- Test result is considered to be an adverse event by the investigator or sponsor.

- Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for bullet point 4.
- Relevant clinically significant laboratory results should be recorded in the patient's CRF.

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the sponsor (or his/her designated representative), or until a diagnosis that explains them is made.

13.3 Causality

Many adverse events that occur in this trial, whether they are serious or not, will be known treatment related toxicities. The Principal Investigator is responsible for the assessment of causality of serious adverse events (see definitions of causality table).

If there is any doubt about the causality of an event, the investigator should inform ICR-CTSU who will notify the Chief Investigator. The drug manufacturer and/or other clinicians may also be asked for advice.

13.4 Severity of Adverse and Serious Adverse Events

Adverse event (AE) severity is a clinical determination of the intensity of an AE and SAEs. The severity assessment for a clinical AE should be completed using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.02). Any AE not listed in the CTCAE will be graded as follows:

Table 4: Severity of Event

Grade	Definition	Description
1	Mild adverse event	Does not interfere with the patient's usual function [awareness of symptoms or signs, but easily tolerated (acceptable)].
2	Moderate adverse event	Interferes to some extent with the patient's usual function [enough discomfort to interfere with the usual activity (disturbing)].
3	Severe and undesirable adverse event	Interferes significantly with the patient's usual function [incapacity to work or to do usual activities (unacceptable)].
4	Life-threatening or disabling adverse event	Results in risk of death, organ damage or permanent disability (unacceptable).
5	Death related to adverse event. Relationship to Study Drug	Event has a fatal outcome.

Causality of Event

A determination should be made by the investigator regarding the relationship (if any) between an AE and the study drug. A causal relationship is present if there is a reasonable possibility that the AE may have been caused by the study drug. The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study.

Table 5: Definitions for Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

The expectedness of a SAR related to the study drug should be assessed by the Chief Investigator in accordance with the information provided in the IB for olaparib.

Expected SARs should be reported as per the SAE reporting guidelines. SAEs should be reported up to 30 days after the patient's last dose of study medication

A summary of 'expected' adverse reactions as stated in the IB is listed below:

Table 6: Expected Adverse Reactions (Olaparib Monotherapy)

Frequency of Adverse Events	Very common	Common	Rare
Grade (G)	Mild to moderate CTCAE:G1-2	Mild to moderate CTCAE:G1-2	Mild to moderate CTCAE:G1-2
Adverse Events	Nausea	Anaemia	Lymphopenia
	Vomiting	Headache	Tachycardia

	Fatigue	Dyspepsia	Thrombocytopenia
		Dizziness	Neutropenia
		Asthenia	
		Decreased appetite	
		Dysgeusia	
		Constipation	

13.5 Procedures for Recording and Reporting Adverse Events

13.5.1 Reporting Serious Adverse Events (SAEs) to ICR-CTSUS

Any SAE that occurs from the time of screening and up to 30 days following the last dose of olaparib must be reported, whether or not considered causally related to the study treatment. For patients that do not enter the trial SAEs should be reported from screening until a decision is made the patient will not enter the trial. Any SAEs reported in this period should be followed until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised

All SAEs should be reported to ICR-CTSUS, within 24 hours of the study team becoming aware of the event, by completing the trial specific SAE forms and faxing to:

The ICR-CTSUS safety desk
Fax no: 0208 722 4368
For the attention of the TOPARP Trial team

Investigators or other site personnel must ensure that:

- All SAE forms must be completed, signed and dated by the Principal Investigator or designated representative.
- All SAE reports are supported by documentation in the patient's medical records. Obtain and maintain in his files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
- All patients with a serious adverse event must be followed up and the outcomes reported in a follow up severe adverse event report form to the ICR CTSUS.
- In the event of fatal or life-threatening AEs where important or relevant information is missing, active follow-up must undertaken immediately.

13.6 Review of Serious Adverse Events (SAEs) or Reactions (SARs)

Reported events / reactions using the SAE forms will be assessed by the Chief Investigator (or designated representative) for causality and expectedness.

NB. The Chief Investigator cannot down grade the Principal Investigator's assessment of causality.

SAEs assessed as having a causal relationship to study drug and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities by ICR-CTSU (see figure 4 for SAE reporting).

Centres should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of the SAE.

13.7 Expedited Reporting of SUSARs

If an SAE is identified as being a SUSAR by the Chief Investigator, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Main REC, the sponsor institutions and AstraZeneca within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the Chief Investigator, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Main REC, the sponsor institutions and AstraZeneca within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA, Main REC, the sponsor institutions and AstraZeneca as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

The Principal Investigators at all actively recruiting centres will be informed of any SUSARs occurring within the trial at regular intervals.

13.8 Follow up of Serious Adverse Events

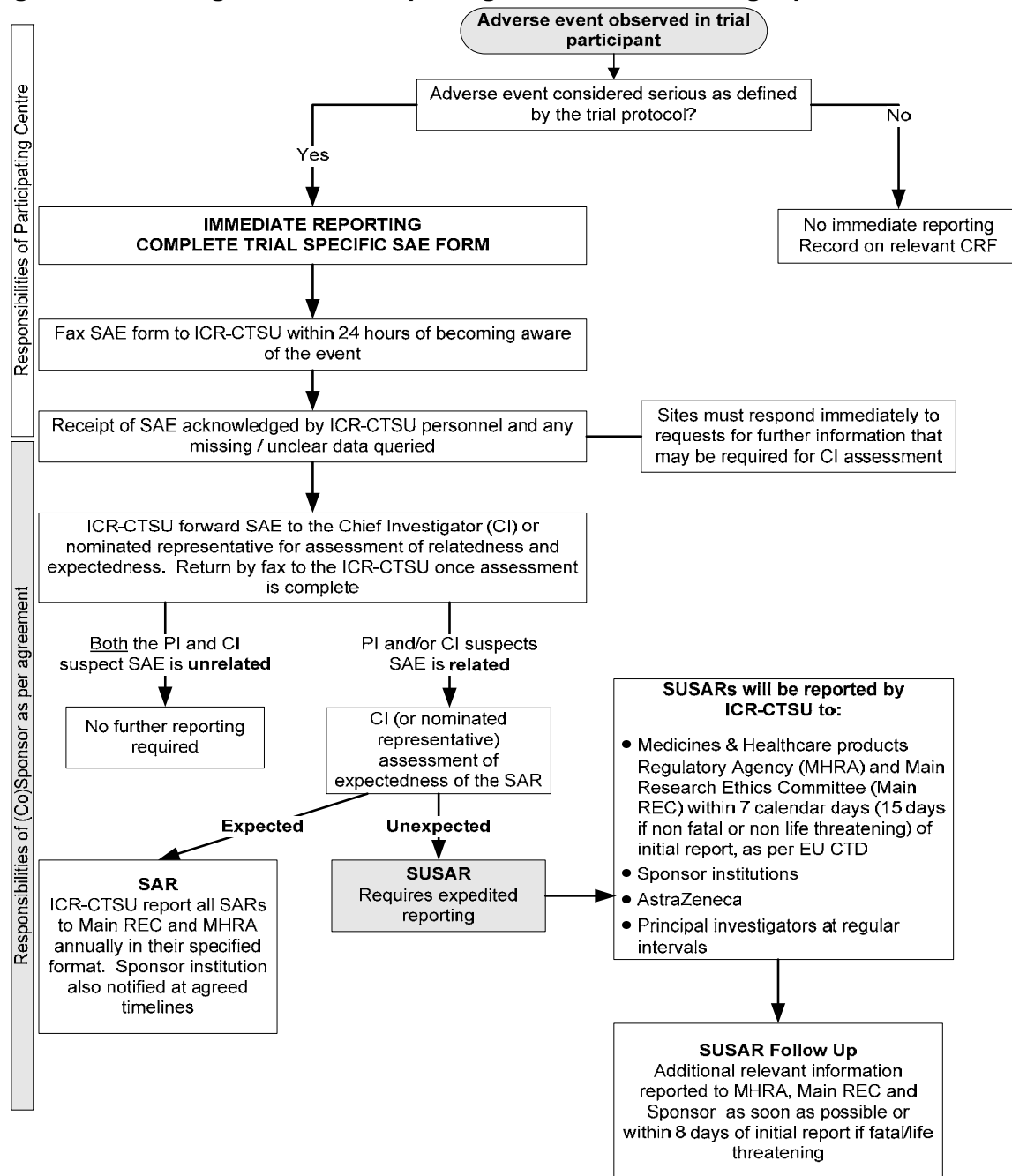
Centres should continue to follow up SAEs until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Information on outcome of the SAE should be completed on the relevant part of the original SAE and faxed to ICR-CTSU as soon as the Principal Investigator becomes aware.

NB Any male patient who fathers a child whilst on study medication must be followed up and the outcome reported to ICR-CTSU who will then forward the details to AstraZeneca.

13.9 Annual Reporting of Serious Adverse Reactions

An annual report will be provided to the MHRA and the Main REC, by ICR-CTSU and copied to the Co-sponsors, on the anniversary of the date when the Clinical Trials Authorisation (CTA) was obtained. This will include all related events reported on SAE forms, and a report from the Independent Data Monitoring Committee (IDMC).

Figure 4: Flow diagram for SAE reporting, and action following report



NB. All SAE's should continue to be followed up as specified in the protocol.

14 STATISTICAL CONSIDERATIONS

14.1 Trial Design

The aim of this design is to look for potentially sensitive subgroups of patients by undertaking a screening trial (part A) followed by a validation trial (part B) if there is evidence a sensitive subgroup exists.

Both of these trials are non-randomised with response rate being assessed at 6 months post registration as the primary endpoint. These trials will be followed by a randomised phase II trial (part C) in the sensitive patient groups with overall survival as the primary endpoint. The aim is to identify a sensitive subgroup with a 50% response rate on the basis that high response rates are necessary to be confident of demonstrating a survival benefit, the primary goal of the phase II strategy.

It is possible that all patients are sensitive to treatment in which case it has to be possible to apply the same efficacy and inefficacy criteria as are used in the validation trial to all patients in the screening trial.

Part A

The screening trial will involve all comers (unselected patients) and is an open-labelled, multi-centre two-stage design based on $H_0: p_0=0.05$; $H_a: p_1=0.20$; $\alpha=0.02$ and $\beta=0.10$. It will recruit a **maximum of 45 patients** (30 in stage 1 and 15 in stage 2) with an initial efficacy level of 20% and an inefficacy level of 5%, to allow for the fact that only a small subset of patients may be sensitive to olaparib.

This part will evaluate the anti-tumour activity of olaparib in unselected CRPC patients and will identify potential biomarkers of response.

- **Stage 1**

The first stage will enrol 30 patients and when all 30 have been followed up for a minimum of 6 months an interim analysis will take place to evaluate the response rate:

Given the efficacy level of 20% and inefficacy level of 5% the trial will be terminated with the conclusion of inefficacy if there are **2 or fewer responses**. If there are **15 or more responses** in the first stage, broad efficacy will be concluded and no more patients will be entered and Part C will commence in unselected patients.

If between **3 to 14 patients respond**, patient accrual will continue to a total of 45 patients (stage 2) and an investigation into the identification of a potential biomarker of response will be carried out.

- **Stage 2**

If the trial progresses to stage 2, a further 15 patients will be recruited, giving a total of 45 patients for part A. An interim analysis will be triggered once 45 patients have been followed up for a minimum of 6 months or alternatively we observe 23 or more responses. The recruitment will be halted.

If **23 or more** patients respond, Part C will be initiated. If **5 or fewer patients** respond, the null hypothesis will be accepted and the study will be terminated. If **between 6 and 22 patients respond**, an investigation into the identification of potential biomarkers of response will be carried out. If a potential biomarker subgroup is found, Part B will be undertaken. If a subgroup is not found, then Part C will be undertaken if at least 19 of the patients have responded, otherwise the study will be terminated since sufficient activity has not been observed based on $H_0: p_0=0.3$; $H_a: p_1=0.5$; $\alpha=0.059$ and $\beta=0.11$.

Deriving a classifier for identification of tumours with high susceptibility to PARPi olaparib in CRPC.

All patients participating in this trial will have their archival tissue, fresh tumour biopsies and circulating tumour cells collected prior to starting olaparib. The primary biomarkers to be evaluated include PTEN loss by IHC and FISH, *ETS* gene rearrangements by FISH and RAD51 foci formation. It should be noted that PTEN loss and *ETS* rearrangements co-associate and are found in approximately 50% of prostate cancers. In addition that is emerging evidence to suggest that RAD51 foci formation is diminished in tumours with HR defects such as those with loss of PTEN and *ETS* rearrangements (15, 27, 41, 44).

See section 2.1 for a discussion of relevant biomarkers.

Biomarkers will be classified as either established markers of sensitivity to synthetic lethality with PARPi (e.g. *BRAC1* *-/-*, *BRAC2* *-/-*), or as exploratory biomarkers. Established biomarkers will have a guaranteed place in the biomarker classifier but exploratory biomarkers will have to be shown to have predictive ability from the trial data.

The correlation between biomarkers will first be examined using Spearman's rank correlation. If two biomarkers are highly correlated or known to be highly correlated from previous evidence one of the biomarkers will be dropped. The use of appropriate cut-points of continuous scores for individual biomarkers will be decided before examining their association with response.

For potential promotion to the classifier, a false discovery rate of 10% or less will be applied to all exploratory biomarkers, using the p-values from the univariate association with response (Fisher's exact test, $p<0.10$ 2-sided). If evidence exists from other sources it may be incorporated into the assessment of specific biomarkers using meta-analysis to give an 'overall' p-value.

Secondly, identification of a multivariable predictive classifier will be undertaken using a significance level of 10% or less for the inclusion of the biomarker in the classifier (logistic regression). In the event of a tie, e.g. two or more classifiers with similar performance, a liberal approach will be adopted on the basis that it will be possible to exclude non-responsive biomarker groups at a later date. Standard prognostic factors may be included in the classifier if they are independent of the biomarkers.

The goal will be to develop a classifier which identifies a group with a response rate of 40% or more on the basis that the levels for inefficacy and efficacy are set at 30% and 50% respectively.

The biomarker defined subgroup satisfying the above criteria will be selected for validation in Part B. If olaparib successfully graduates from this, stage Part C will be undertaken. If convincing evidence arises from other translational studies of olaparib or other PARP inhibitors the IDMC will be asked to advise whether or not an analysis should take place.

Part B

The biomarker status of patients registered in Part B will be evaluated and only patients with the presence of the putative biomarker subgroup identified in Part A will be entered. Forty-four additional patients will be treated in this single stage, which assumes $H_0: p_0=0.3$; H_a ; $p_1=0.5$; $\alpha=0.05$ and $\beta=0.15$.

If **19 or more** of the **44 patients** respond (43%), then a proposal for a subsequent randomised controlled trial to investigate the predictive potential of the biomarker will be developed. If **18 or less** patients respond, the study will be terminated.

Further information regarding the sample size calculations of both parts A and B is shown in Appendix A. The detectable effects in the biomarker sensitive group assuming 80% power are presented on Appendix B.

14.2 Analysis populations

Analysis populations are defined as follows:

- **Intention to treat (ITT):** This population includes all patients enrolled into the study regardless of whether they are later found to be ineligible, a protocol violator, never treated or not evaluated. Patients for whom the primary endpoint cannot be evaluated will be treated as non-responders.
- **Evaluable-patient population:** This population contains all enrolled patients for whom the primary endpoint can be evaluated. A patient will be “evaluable” if **at least a bone scan or RECIST measurement is available. Where evaluability is difficult to define the final decision will rest with the IDMC.**
- **Per protocol (PP):** This population contains all enrolled patients who received at least 1 cycle of olaparib without major protocol violations.
- **Safety population:** This population includes all enrolled patients who received at least 1 dose of olaparib.

The analysis of the primary outcome will use the evaluable-patient population with sensitivity analyses in the ITT and per protocol populations. All other analyses will use the ITT population. The ITT and PP analyses will treat non-evaluable patients as non-responders. The safety population will be used to further characterise the safety profile of olaparib in advanced CRPC patients.

14.3 Primary Efficacy Endpoint

Response will be defined by:

- Objective response by modified RECIST (baseline lymph node size must be ≥ 2 cm to be considered a target lesion) (Appendix E) and / or
- Conversion of circulating tumour cell count (CTC) to $< 5/7.5$ ml blood nadir confirmed by at least two readings 4 weeks apart and / or
- PSA decline of $\geq 50\%$ (according to the PCWG2) (Appendix D)

Failure will be defined as:

- Progression by RECIST- increase in measurable lesion size(S) or new lesion AND/OR
- Progression by bone scan – see Appendix D

Response will be evaluated 6 months post registration. The last value of PSA, CTC count, CT scan and bone scan on or up to four weeks before the date of first study treatment will be used as the baseline value for this assessment. The response rate will be presented along with its exact two-sided 95% confidence interval.

14.4 Secondary Efficacy Endpoints

The following endpoints will be assessed 6 months post registration. However, decisions made within the trial to comply with the adaptive design will not necessarily require 6 months follow up on all patients, e.g. it may be possible to enter patients into the second stage of Part A when it is clear between 3 and 14 responses will occur in the first stage even though not all 30 patients have 6 months follow up.

PSA response and PSA progression are defined according to the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA value from cycle 1 day 1 (baseline). This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. The first PSA reading will be obtained at week 12.

Time-to-PSA Progression

For patients who have achieved a $\geq 50\%$ decrease from the cycle 1 day1 (baseline), the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the **nadir** is documented. This must be confirmed by a second consecutive value obtained 4 or more weeks later. For patients without a PSA decrease of this magnitude or no decrease at all, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the **baseline** is documented. This must also be confirmed by a second consecutive value 4 or more weeks later. Time to PSA progression will be summarised using Kaplan-Meier methods.

Duration of PSA response

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the cycle 1 day 1 (baseline) value (must be confirmed by a second value) until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be assessed at the last PSA measurement. Duration of PSA response will be summarised by the median and presented along its 95% confidence interval.

PSA objective response rate (PSA-ORR)

The proportion of patients having achieved partial or complete response defined by PSA will be reported with the corresponding exact two-sided 95% confidence interval.

Pattern of PSA Responses

Waterfall plots will be presented (as per PCWG2 recommendations) that show the percentage of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy), as well as the maximum decline in PSA that occurs at any point after treatment. Waterfall plots provide a broader display of PSA changes than dichotomised responses.

CTC Response

The proportion of patients with a CTC conversion to $<5/7.5$ ml blood at nadir (confirmed by two readings at least 4 weeks apart) will be presented along an exact two-sided 95% confidence interval. Its association with PFS and OS will be examined via Cox regression models first univariately and subsequently in a multivariable model adjusting for potential confounders. Waterfall plots of CTC falls will also be presented that show the percentage change in CTC counts from baseline to 12 weeks as well as maximal CTC count declines that occur at any point after treatment.

The following endpoints will be evaluated using Kaplan and Meier methods:

Radiographic Progression Free Survival (rPFS)

Radiographic progression free survival (rPFS) will be defined by either RECIST progression and /or progression on bone scan (Appendix D and E). It will be measured from the date of trial entry to the first occurrence of radiographic progression or death from any cause. If no event exists, then rPFS will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Time to Radiographic Progression

Time to radiographic progression (progression defined by either RECIST progression and /or progression on bone scan) will be measured from the date of trial entry to the first occurrence of radiographic progression. Death from prostate cancer or any other cause without prior radiographic evidence of progression will not count as an event. If no event exists, then time to radiographic progression will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Progression Free Survival (PFS)

Progression free survival will be measured from the date of trial entry until radiographic progression, unequivocal clinical progression or death. If no event exists, then PFS will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Overall Survival (OS)

OS will be measured from the date of trial entry to the date of death (whatever the cause). Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow-up.

14.5 Tertiary/exploratory Endpoints

- **Pain palliation:**

Pain palliation will be assessed using the Brief Pain Inventory's (BPI Short Form) worst pain intensity score and average score. A composite of the four pain items (worst, least, average, right now) will be presented as supplemental information. Change in BPI score from baseline will be assessed at 6 months post registration. A reduction of two points in the worst pain score relates to an improvement of pain. The analgesic relief received will be described.

- **Safety Endpoint**

Safety analysis will be summarised using the safety population. Extent of exposure to study drug will be summarised and details will be provided. Treatment emergent adverse

events (AEs) are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose. Adverse events will be graded according to the NCI-CTCAE v4.02. Adverse events will be summarised by grade, according to the worst grade experienced. In addition, most frequently observed AEs will be summarised. In the summary of AE, an AE occurs more than once within a SOC and PT will be counted only once using the worst grade experienced. Serious AE and deaths observed within 30 days of the last dose of study treatment will be provided in a listing.

All adverse events resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of study drug will also be listed and tabulated by preferred term. Clinical laboratory test results will be collected pre-treatment and through 30 days post last dose of study treatment. All laboratory test results will be classified according to the NCI CTCAE v4.02 criteria. Standard reference ranges will be used for missing or discrepant normal ranges. Baseline laboratory test values are the results from the last blood samples drawn on or prior to the first day of study treatment. On-study laboratory test values are those results from blood samples drawn a day after the first study treatment up until 30 days after the last dose of study treatment.

- **Impact of treatment with olaparib on bone metastases imaging by DW-MRI.**

Diffusion-weighted MRI scan will be offered to patients recruited in part A and we expect approximately 50% acceptance rate. This analysis will be **purely exploratory** and we will examine whether response to olaparib expressed by changes in apparent diffusion coefficients produced by the DW-MRI scan correlate with 1) PSA decline, 2) CTC conversion and 3) radiological responses coming from conventional imaging. In 20 patients it is possible to detect a correlation coefficient of 0.6 which is equivalent to the parameter explaining 36% of the variation using a 2-sided 5% significance level.

14.6 Data Monitoring

An Independent Data Monitoring Committee will meet in confidence at regular intervals, firstly to review the safety analysis following the first 5 and 10 patients recruited and subsequently every 6 months (or at intervals determined by them) to review accrual, safety and efficacy data.

The replacement of patients who withdraw from the study or who are un-evaluable for reasons deemed not to be treatment related will be based on the advice of the committee. The committee will review the results of each interim analysis (progression from stage 1 to stage 2 and progression to part B) and will be asked to advise. For completeness a sensitivity analysis of the progression free rate calculated by the Kaplan Meier product limit method will also be presented in which withdrawals and deaths are censored. The summary statistic will be the progression free rate at 6 months together with its 95% one-sided confidence interval.

15 TRANSLATIONAL RESEARCH

Paraffin embedded tumour blocks or unstained sections from archival tumour tissue from the time of the original diagnosis or from a biopsy / resection of metastatic disease will be required from all subjects who enrol on the study. Patients who do not have adequate archival tumour tissue will be required to have tumour confirmed in a repeat tumour biopsy in order to be enrolled on the study. CTCs, urine, plasma samples and mandatory fresh tumour biopsies will be obtained at various time points during the study (Table 2 & 7). CTCs will be enumerated to evaluate conversion rates (CTC from ≥ 5 cells/7.5ml blood at baseline to < 5 cells/7.5mls) on this treatment. The tumour tissue will be assessed for multiple biomarkers including *PTEN* and *ERG* expression, *PTEN* deletions, *TMPRSS2-ETS* gene rearrangements using multicolour FISH studies, markers of DNA damage and HR repair such as γ H2AX and RAD51 focus formation, markers of tumour cell proliferation and cell cycle phase. Blood samples for plasma-based biomarker will be utilised for several studies including obtaining normal germline DNA and circulating tumour DNA for mutational analysis (e.g. *BRCA1*, *BRCA2*, *CHEK2*, etc.), quantitative real time polymerase chain reaction for *ERG* detection, proteomics, metabolomics, RNA and microRNA (miRNA) studies. Urine samples will be utilised to evaluate metabolomics, RNA and urine telopeptides profiles. Additional putative predictive biomarkers involved in the HR DNA repair pathway and sensitivity to PARP inhibition may be evaluated to facilitate the characterisation optimal determinants of response and resistance to olaparib treatment. Some of these additional markers/studies may come from other translational studies.

All the tumour tissue, CTC, plasma and urine samples will be sent to the Institute of Cancer Research Biomarker Group for processing and analysis. Some of these samples may be labelled with the patients' initials, hospital pathology number and trial number when they are sent to the research laboratory. When they arrive at the laboratory each sample will be coded with a unique anonymised number and any personal details removed. The number generated is linked to the patient trial ID held at the ICR CTSU. This coding system will maintain patient confidentiality whilst allowing biological details to be compared to treatment findings.

Samples will be stored in a secure area in the Cancer Biomarkers Laboratory at the Institute of Cancer Research. Samples will only be accessible by accredited staff involved in the processing and analysis of the samples. Some of the tumour/plasma samples collected may need to be sent to another site for processing and analysis. This will only occur following an established agreement being set up and assurance that patient confidentiality is maintained. **Instructions for the sample requirements, collection, handling, labelling, shipment and storage will be provided in a reference Laboratory Manual for Investigators.**

In some cases the archival tumour blocks will be returned to the local laboratories after the study is complete, depending on local practice. Patients participating on this study will be asked to give permission for possible future research into prostate cancer using these samples. The confidential nature of the tissue and associated data will be fully protected, and any other research using your tissue will first be reviewed and approved by an ethics committee.

These tumour and plasma samples may be used for, but not restricted to, the elucidation of mechanism of response, understanding the mode of action of olaparib and improving the understanding of disease progression.

Archival Tumour Blocks and Fresh Biopsies

An adequately sized (minimum of 2 mm x 2 mm) archival tumour tissue paraffin block from resection or a core biopsy from the time of the original diagnosis or from a biopsy / resection of metastatic disease at any time prior to study entry is required. Alternatively, unstained slides prepared from the block can be provided. Mandatory fresh biopsies should be obtained at baseline (during the screening period; anytime between Day-28 to Day1), post commencement of treatment (during Cycle 1; anytime between Day 8 and Day 28) and at study discontinuation. The third biopsy is optional and will be obtained at any point between the patient coming off study treatment to the end of treatment visit.

The fresh tumour biopsy may be obtained from either the prostate or a metastatic site that is safe and amendable to a biopsy. Tumour biopsies may be obtained from the prostate itself (if it has not been surgically resected and has not been treated with radiotherapy) via an ultrasound-guided transrectal biopsy. Local recommendations for the procedure will be followed. Alternative sites where a biopsy can be obtained include lymph nodes, bone or liver where there is evidence of cancer on imaging. Patients who do not have evidence of visceral disease but do have evidence of bone metastasis on the bone scan may undergo a bone biopsy and aspirate from the ischium. Biopsies will be performed under radiological guidance as a day case whenever feasible. Ideally, the pre- and post-treatment biopsies will be from the same site. Collecting, handling procedures, shipping requirements and storage conditions will be provided in the TOPARP Laboratory Manual.

Circulating Tumour Cell (CTC) Assessments

A total of 18 blood samples will be drawn over 9 study visits for each patient enrolled during the first 12 months of treatment. Baseline samples will be collected at screening and one Cycle 1 Day 1 and subsequently CTC blood samples will be collected at Cycle 1 day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, every third cycle thereafter and at time of discontinuation of study treatment. CTCs will be enumerated using Veridex CellSearch™ platform. Patients being enrolled at the Royal Marsden NHS Foundation Trusts will have an additional 2 samples collected; an additional sample at screening and at Cycle 1 Day 1 (Table 7). CTC samples in all patients will be used to enumerate CTC counts and evaluate the molecular profile of tumour cells. Samples will be collected and shipped according to specified detail in the TOPARP Laboratory Manual. Amongst the molecular markers that will be studied include:

Immunofluorescence: PTEN, ERG, RAD51, γ H2AX and markers of tumour cell proliferation and cell cycle phase.

FISH: Including *PTEN*, *TMPSS2/ERG*

Plasma and Urine-Based Biomarkers

Plasma and urine samples for different analyses will be collected at multiple time points during the study (refer to Table 7 for details on the specific samples). These samples will be utilised for the purpose of analysing circulating plasma biomarkers including circulating tumour DNA and RNA for mutational analyses, quantitative real time polymerase chain reaction of ERG detection, plasma proteomic signature, plasma and urine metabolomic studies and microRNA (mirRNA) profiles. Proteomic, metabolomic and miRNA profiling may generate signatures that can be used as predictive, prognostic and pharmacodynamic biomarkers that may also be correlated with other study endpoints. Samples will be collected and processed according to specified detail in the TOPARP Laboratory Manual.

LC-MS metabonomics: Blood and urine samples will be obtained at screening, on Cycle 1 Day 1 (pre-dose and 2hour post-dose), Cycle 1 Day 8 (pre-dose and 1hour post-dose), and Day 1 of subsequent cycles 2, 3 and 6 (-5 min pre-dose and 2hour post-dose).

PAXgene miRNAs Analyses: Whole blood samples will be collected at screening, Cycle 1 Day 1, and Day 1 of subsequent cycles 3, 5 and at either treatment discontinuation or the end of treatment visit.

Proteomic profiling: Plasma samples will be obtained at screening, Cycle 1 Day 1 (pre-dose) and at either treatment discontinuation or the end of treatment visit.

Circulating Plasma DNA and RNA: Plasma samples will be collected at screening, Cycle1 Day 1, Cycle 1 Day 8 and on Day 1 of Cycles 2, 3, 5 and at either treatment discontinuation or the end of treatment visit.

Urine Markers of Bone Turnover (telopeptides): 24 hour urine samples will be collected at screening, Cycle 1 Day 1 and Cycle 3 Day1, Cycle 6 Day 1 and at either treatment discontinuation or the end of treatment visit.

Diffusion-weighted MRI

Diffusion-weighted MRI (DW-MRI) will be performed on an optional basis in a subset of patients. DW-MRI provides better visualisation of tumour cellularity and the results of DW-MRI will be correlated with bone scan results, PSA, CTC counts and patient outcome.

The intent of the biomarker / translational research embedded in this protocol is outlined below:

- To characterise the molecular profile of prostate cancer and sub-divide this heterogeneous disease.
- To develop predictive biomarkers of olaparib sensitivity which may be utilised to optimise patient selection for future studies
- To correlate the molecular profile of prostate cancer (in particular but not exclusively *PTEN*, *ERG* status by both IHC and FISH analysis) with clinical outcome
- To determine target modulation from olaparib treatment by the generation of γ H2AX foci formation, a marker of DNA damage in fresh biopsies and CTCs

- To evaluate the utility of early changes to CTC counts as a surrogate of clinical benefit to PARP inhibitors in CRPC
- To correlate CTC changes with PSA and radiological responses to olaparib treatment in CRPC

TIME POINTS	BLOOD BASED BIOMARKERS						URINE BIOMARKERS
	CTC	Plasma DNA & RNA Analyses	PAXgene miRNA	Plasma Proteomic Profile	Plasma Metabonomic Profiling	Urine Metabonomic profiling	Bone markers of turnover
Screening*	2x10mls	3x10mls	1x2.5mls	1x10mls	2x6mls	2 samples	24 urine collection
Cycle 1 day 1*	2x10mls	3x10mls	1x2.5mls	1x10mls	2x6mls	2 samples	24 urine collection
Cycle 1 day 8	2x10mls				2x6mls	2 samples	
Cycle 1 day 15	2x10mls						
Cycle 2 day1	2x10mls	3x10mls			2x 6mls	2 samples	
Cycle 3 day1	2x10mls	3x10mls	1x2.5mls		2x6mls	2 samples	24 urine collection
Cycle 4day1	2x10mls						
Cycle 5 day1		3x10mls	1x2.5mls				
Cycle 6 day1					2x6mls	2 samples	24 urine collection
Cycle 7day1 & every 3rd cycle thereafter	2x10mls						
End of Treatment Visit	2x10mls	3x10mls	1x2.5mls	1x10mls	2x6mls	1 sample	24 urine collection

Table 7: Summary of the blood and urine-based biomarker samples for the translational research

* Patients recruited at the Royal Marsden NHS Foundation Trusts will have an additional (3x10mls) CTC sample collected at screening and Cycle1Day1.

For total volumes of safety and research bloods refer to Appendix J.

16 TRIAL MANAGEMENT

The trial will be coordinated by ICR-CTSU in accordance with their quality management system.

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, Co-investigators and identified collaborators, the Trial Statistician and the Trial Managers. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of centres and professional groups. Notwithstanding the legal obligations of the Co-Sponsors and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. Where possible, membership will include a lay/consumer representative. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and will include an independent Chairman (not involved directly in the trial other than as a member of the TSC) and not less than two other independent members. It is the role of the TSC to monitor progress of the trial and to ensure there is adherence to the protocol and the principles of Good Clinical Practice. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16.3 Independent Data Monitoring Committee (IDMC)

An IDMC will be instigated to monitor the progress of the trial. Membership of the IDMC will be proposed by the TMG and approved by the TSC. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU. The IDMC should meet in confidence at regular intervals, firstly to review the safety analysis following the first 5 and 10 patients recruited and at least every 6 months following. A report of the findings and recommendations will be produced following each meeting. This report will be submitted to the TMG and TSC, and if required, the main REC and the MHRA.

The IDMC reserve the right to release any data on outcome or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

17 RESEARCH GOVERNANCE

This Clinical Trial will be conducted in accordance with the ethical principles laid down by the Declaration of Helsinki, 1964 and as amended in 1996 and the principles of Good Clinical Practice.

17.1 Sponsor Responsibilities

The Co-sponsors are The Institute of Cancer Research (ICR) and The Royal Marsden NHS Foundation Trust (RMH). Sponsorship activities and delegated responsibilities are shared between ICR and RMH, in accordance with The Medicines for Human Use (Clinical Trials)

Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. Responsibilities of the Co-sponsors are set out in an agreement letter between ICR and RMH.

17.2 Principal Investigator Responsibilities

Responsibilities of each Principal Investigator and participating centre will be detailed in a contract with the Co-sponsors.

Principal Investigator responsibilities include putting and keeping in place arrangements to run the trial at their site according to the trial protocol and applicable guidance notes, The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. The above responsibilities include, but are not limited to, the following:

- Putting and keeping in place arrangements to adhere the principles of GCP
- Keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving and destruction of documentation once the trial has ended as required by regulation 31 of the principal Regulations of the Medicines for Human Use (Clinical Trials) Regulations 2004 implementing the commission directive 2005/28EC
- Ensuring investigational medicinal products (IMPs) are made available to subjects free of charge
- Taking appropriate urgent safety measures and
- Ensuring recording and prompt reporting of SAEs/SARs to ICR-CTSU

ICR is responsible for co-ordinating any required legal agreements and investigator statements.

The delegation of sponsorship responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership and as such it is necessary to share pertinent information between ICR and RMH/Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

17.3 AstraZeneca Responsibilities

AstraZeneca are responsible on behalf of the co-sponsors for the manufacture, packing, labelling and distributing of study drug and matching placebo to site in accordance with Good Manufacturing Practice and all applicable local legislation. Some of these responsibilities have been delegated by AstraZeneca to Fisher Clinical Services. Responsibilities are defined in an agreement between AstraZeneca and the co-sponsors, and AstraZeneca and Fisher Clinical Services.

18 TRIAL ADMINISTRATION & LOGISTICS

18.1 Protocol Compliance

The TOPARP Trial is being conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the EU Clinical Trials Directive. Before activating the trial, participating centres are required to sign an agreement accepting responsibility for all trial activity which takes place within their centre.

Sites may commence recruitment once centre agreements have been signed by both parties, trial documentation is in place and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

18.2 Data Acquisition

ICR-CTSU is responsible for the data management and statistical analysis of trial data. Electronic (e) Case Report Forms (CRF) will be used for the collection of trial specific data. The Trial Management Group reserves the right to amend or add to the CRF as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres in accordance with the guidelines provided by ICR-CTSU.

The clinical data should be recorded in the TOPARP eCRFs in a timely manner.

By participating in the TOPARP trial, the Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure that:

- Sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs;
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- All staff at their centre who are involved with the trial will meet the requirements of the EU Directive;
- Original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent;
- All essential documents must be retained for five years after the Trial ends to comply with current legislation.
- Staff will comply with the protocol and Trial Guidance Notes for the TOPARP trial.

Completion of eCRFs will be monitored by ICR-CTSUS, CRFs and any missing forms will be reported to the originating site.

18.3 Central Data Monitoring

Once data has been entered by the site personnel on the eCRF, the ICR-CTSUS will review and check the data for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be issued to the centre for resolution.

Data will be further reviewed for data anomalies / missing data, by central statistical monitoring. Any systematic inconsistencies identified may trigger monitoring visits to centres.

18.4 On-Site Monitoring

Site monitoring will be conducted at participating centres at least once during the course of the trial. Additional on-site monitoring may be triggered by routine central statistical monitoring or identification of a new risk to the trial.

If a monitoring visit is required, ICR-CTSUS will contact the centre to discuss dates of proposed visit. Once a date has been confirmed, the centre should ensure that the relevant patient notes are available for monitoring.

If any problems are detected in the course of the monitoring visit, ICR-CTSUS will work with the Principal Investigator to resolve issues and, if necessary, to determine the centre's future participation in the study.

ICR-CTSUS staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the site agreement and trial protocol to ensure the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996.

18.5 End of trial

The end of trial for MHRA and MREC purposes is the date of last data capture

18.6 Archiving

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. Essential documents will be maintained at ICR-CTSUS in a way that will facilitate the management of the trial, audit and inspection. They should be retained for a sufficient period (at least 15

years) for possible audit. Documents should be securely stored and access restricted to authorised personnel.

19 PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

The trial will have received ethical, regulatory and institution specific approvals prior to recruitment of any patients into the study. Before entering patients, the Principal Investigator at each site is responsible for gaining Site Specific Assessment and Research and Development approval of this protocol.

Patients should be asked to sign the trial consent forms after receiving both verbal and written information about the trial. All consent forms must be countersigned by the Principal Investigator or a designated individual. A record listing the designated individuals and the circumstances under which they may countersign consent forms must be clearly documented at the research site as part of the Delegation of Responsibilities Log. This log, together with original copies of all signed patient consent forms, must be available for inspection.

The TOPARP patient information sheets should be provided in addition to any standard patient information sheets that are provided by the centre and used in routine practice.

19.1 Patient Confidentiality

Patients will be asked to consent to their full name being collected at registration in addition to their date of birth, hospital number, postcode and NHS number (CHI in Scotland) to allow tracing through national records to assist with long term follow up and to allow linkage with routinely collected NHS data. The personal data recorded on all documents will be regarded as confidential, and any information which would allow individual patients to be identified will not be released into the public domain.

Each investigator should keep a separate log of all patients' Trial IDs, names, addresses and hospital numbers. The investigator must maintain trial documents, which are to be held at the participating centres (e.g. patients' written consent forms), in strict confidence. The investigator must ensure the patients' confidentiality is maintained.

ICR-CTSU will maintain the confidentiality of all patients and will not reproduce or disclose any information by which patients could be identified. Representatives of ICR-CTSU and the regulatory authorities will be required to have access to patients notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries it is also necessary to have access to the complete study records provided that patient confidentiality is protected.

19.2 Data Protection

ICR-CTSU will comply with all applicable data protection laws. Any requests from patients for access to data about them held at ICR-CTSU should be directed to the Trial Manager in the first instance who will refer the request to the Data Protection Officer at The Institute of Cancer Research.

19.3 Liability

The Co-Sponsors have taken out an insurance policy to cover their study responsibilities, and certification of this will be provided to the regulatory authorities as required. ICR-CTSU will need to be satisfied that all participating sites have appropriate indemnity arrangements in place.

20 FINANCIAL MATTERS

The trial is investigator designed and led and has been approved by Clinical Trials Advisory & Awards Committee (CTAAC) of Cancer Research UK, and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

ICR has received funding from Cancer Research UK and AstraZeneca (via the AstraZeneca/NCRN collaboration) for the central coordination of the trial. AstraZeneca are also providing olaparib for the purposes of this trial free of charge.

In the UK, the trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research (NIHR) portfolio by virtue of its approval by CTAAC. Therefore, National Cancer Research Network (NCRN) resources should be made available for the TOPARP trial to cover UK specific research costs.

21 PUBLICATION POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group led by the chief investigator, appointed from amongst the Trial Management Group, and participating clinicians. All participating centres and clinicians will be acknowledged in this publication together with the dedicated staff from the ICR-CTSU. All presentations and publications relating to the trial must be authorised by the Trial Management Group, on whose behalf publications should usually be made. Authorship of any secondary publications e.g. relating to the various biological studies will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present

or attempt to publish data relating to the TOPARP trial without prior permission from the Trial Management Group.

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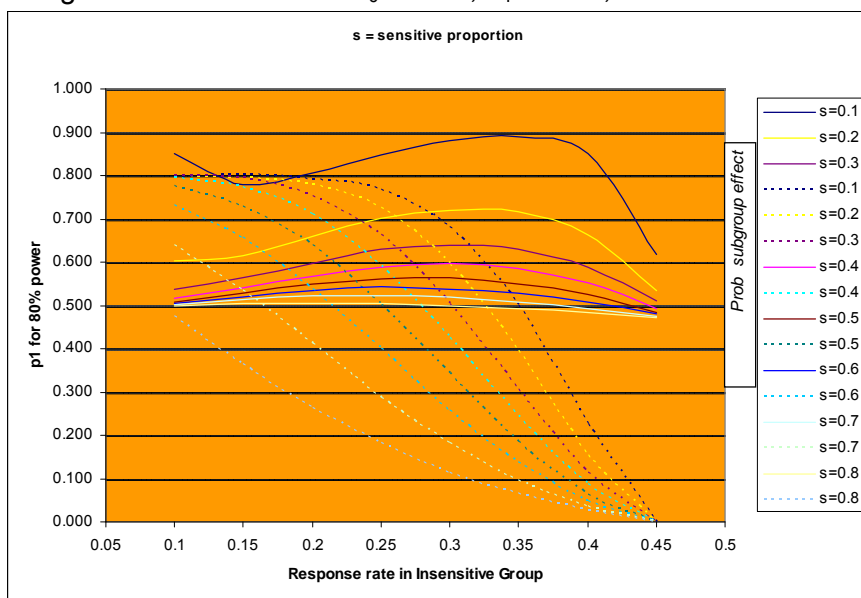
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23 APPENDICES

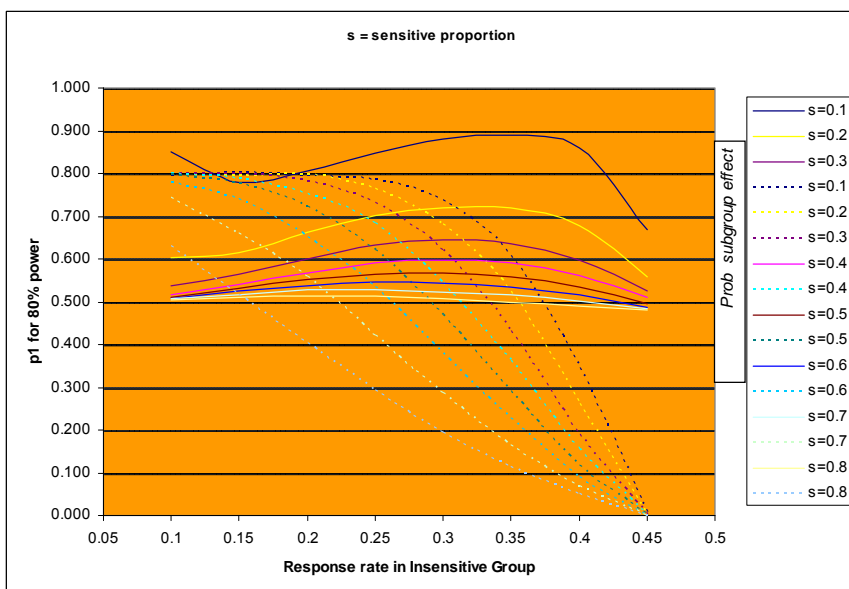
23.1 Appendix A: Detectable Effects

It is possible to calculate detectable effects in the sensitive group (80% power, y-axis) based on the proportion of sensitive patients (individual lines) and the response rate (x-axis) in the insensitive subgroup. Also shown is the probability a subgroup effect is detected (dashed lines), with 80% power this probability cannot exceed 80%. The fall in the probability of detecting a subgroup effect with increasing response rate in insensitive patients is therefore balanced by an increase in the probability of detecting an overall effect. Thus, in the extreme, if the response rate in insensitive patients is 45% and the response rate in sensitive patients is about 50% a conclusion of overall efficacy will be reached with 80% power, for subgroups of size 30% or more.

Using cut offs for Part A of $a_0=15/30$, $a_1=23/45$, as intended.



Using cut offs for Part A of $a_0=18/30$, $a_1=27/45$ the probability of detecting a subgroup effect if the sensitive group is large (>50%) can be improved.



23.2 Appendix B: Sample Size Calculations

TOPARP sample size calculations, **Part A** : alpha 2.2%, Power 90%

Ho : Null Hypothesis Response rate (p0) is 5%

Probability reject **0.97818** *alpha* 2.2%

Reject first stage **0.81218** (Probability of early termination, sum of values in light blue)

Reject second stage **0.166** (sum of values in dark blue)

sum 0.97818

N	po	N second stage														
First		0	1	2	3	4	5	6	7	8	15				
0	0.214639	0.46329	0.3657562	0.13475	0.03073	0.00485	0.00056	4.9E-05	3.3E-06	1.8E-07	3.1E-20				
1	0.338903	0.059	0.046	0.017	0.004	0.001	0	0	0	0	0				
2	0.258637	0.021	0.017	0.006	0.001	0	0	0	0	0	0				
3	0.12705	0.006	0.005	0.002	0	0	0	0	0	0	0				
4	0.045136	0.001	0.001	0	0	0	0	0	0	0	0				
5	0.012353	0	0	0	0	0	0	0	0	0	0				
6	0.002709	0	0	0	0	0	0	0	0	0	0				
7	0.000489	0	0	0	0	0	0	0	0	0	0				
8	7.4E-05	0	0	0	0	0	0	0	0	0	0				
9	9.52E-06	0	0	0	0	0	0	0	0	0	0				
10	1.05E-06	0	0	0	0	0	0	0	0	0	0				
11	1.01E-07	0	0	0	0	0	0	0	0	0	0				
12	8.39E-09	0	0	0	0	0	0	0	0	0	0				
13	6.11E-10	0	0	0	0	0	0	0	0	0	0				
14	3.91E-11	0	0	0	0	0	0	0	0	0	0				
15	2.19E-12														
16	1.08E-13														
17	4.69E-15														
18	1.78E-16														
.....															
26	3.33E-30														
27	2.59E-32														
28	1.46E-34														
29	5.31E-37														
30	9.31E-40														

Stage I 2.31E-12
probability of incorrect stopping

H1 : Null Hypothesis Response rate (p1) is 20%

Probability reject **0.10318** *Power* 89.7%

Reject first stage **0.04418** (Probability of early termination, sum of values in light blue)

Reject second stage **0.059** (sum of values in dark blue)

N	po	N second stage														
First		0	1	2	3	4	5	6	7	8	15				
0	0.001238	0.03518	0.1319414	0.2309	0.25014	0.1876	0.10318	0.04299	0.01382	0.00345	3.3E-11				
1	0.009285	0.003	0.01	0.018	0.02	0.015	0.008	0.003	0.001	0	0				
2	0.033656	0.005	0.017	0.031	0.033	0.025	0.014	0.006	0.002	0	0				
3	0.078532	0.006	0.023	0.04	0.043	0.032	0.018	0.007	0.002	0.001	0				
4	0.132522	0.006	0.024	0.041	0.045	0.034	0.019	0.008	0.002	0.001	0				
5	0.172279	0.005	0.02	0.036	0.038	0.029	0.016	0.007	0.002	0.001	0				
6	0.179457	0.004	0.015	0.026	0.028	0.021	0.011	0.005	0.002	0	0				
7	0.153821	0.002	0.009	0.016	0.017	0.013	0.007	0.003	0.001	0	0				
8	0.110559	0.001	0.005	0.008	0.009	0.007	0.004	0.002	0	0	0				
9	0.067564	0.001	0.002	0.004	0.004	0.003	0.002	0.001	0	0	0				
10	0.035471	0	0.001	0.001	0.002	0.001	0.001	0	0	0	0				
11	0.016123	0	0	0.001	0.001	0	0	0	0	0	0				
12	0.006382	0	0	0	0	0	0	0	0	0	0				
13	0.002209	0	0	0	0	0	0	0	0	0	0				
14	0.000671	0	0	0	0	0	0	0	0	0	0				
15	0.000179														
16	4.19E-05														
17	8.63E-06														
18	1.56E-06														
.....															
26	7.53E-15														
27	2.79E-16														
28	7.47E-18														
29	1.29E-19														
30	1.07E-21														

Stage I 0.000231
probability of incorrect stopping

TOPARP sample size calculations, **Part A**, rule to be applied if no subgroup is found:

Ho : Null Hypothesis Response rate (p0) is 30%

<u>N</u>	<u>p0</u> 0.3	Reject first stage	0.94505 (sum of values in light blue)	alpha	5.5%
0	1.07E-07	16	0.0896266	32	1.3E-08
1	2.06E-06	17	0.0655253	33	2.2E-09
2	1.95E-05	18	0.0436835	34	3.3E-10
3	0.00012	19	0.0266043	35	4.5E-11
4	0.000538	20	0.0148224	36	5.4E-12
5	0.00189	21	0.0075624	37	5.6E-13
6	0.005401	22	0.0035357	38	5E-14
7	0.012895	23	0.0015153	39	3.9E-15
8	0.026251	24	0.0005953	40	2.5E-16
9	0.046252	25	0.0002143	41	1.3E-17
10	0.071361	26	7.065E-05	42	5.3E-19
11	0.09731	27	2.131E-05	43	1.6E-20
12	0.118162	28	5.87E-06	44	3.1E-22
13	0.12855	29	1.475E-06	45	3E-24
14	0.125927	30	3.371E-07		
15	0.111535	31	6.991E-08		

Ha : Alternate Hypothesis Response rate (p1) is 50%

<u>N</u>	<u>p1</u> 0.5	Reject first stage	0.11635	Power	88.4%
0	2.84E-14	16	0.0183782	32	0.00207
1	1.28E-12	17	0.0313511	33	0.00082
2	2.81E-11	18	0.0487684	34	0.00029
3	4.03E-10	19	0.0693024	35	9.1E-05
4	4.23E-09	20	0.0900931	36	2.5E-05
5	3.47E-08	21	0.1072537	37	6.1E-06
6	2.31E-07	22	0.1170041	38	1.3E-06
7	1.29E-06	23	0.1170041	39	2.3E-07
8	6.13E-06	24	0.1072537	40	3.5E-08
9	2.52E-05	25	0.0900931	41	4.2E-09
10	9.07E-05	26	0.0693024	42	4E-10
11	0.000288	27	0.0487684	43	2.8E-11
12	0.000817	28	0.0313511	44	1.3E-12
13	0.002075	29	0.0183782		
14	0.004743	30	0.0098017		
15	0.009802	31	0.0047428		

TOPARP sample size calculations, **Part B** :

Ho : Null Hypothesis Response rate (p0) is 30%

<u>N</u>	<u>p0</u> 0.3	Reject first stage	0.95628 (sum of values in light blue)	alpha	5%
0	1.53E-07	16	0.0825133	32	5.4E-09
1	2.88E-06	17	0.0582447	33	8.4E-10
2	2.66E-05	18	0.037443	34	1.2E-10
3	0.000159	19	0.0219591	35	1.4E-11
4	0.0007	20	0.0117638	36	1.5E-12
5	0.0024	21	0.0057619	37	1.4E-13
6	0.006687	22	0.0025816	38	1.1E-14
7	0.015556	23	0.0010583	39	7.4E-16
8	0.030835	24	0.0003969	40	4E-17
9	0.05286	25	0.0001361	41	1.7E-18
10	0.07929	26	4.261E-05	42	5.1E-20
11	0.105033	27	1.218E-05	43	1E-21
12	0.123789	28	3.168E-06	44	9.8E-24
13	0.130591	29	7.491E-07		
14	0.123928	30	1.605E-07		
15	0.106224	31	3.107E-08		

Ha : Alternate Hypothesis Response rate (p1) is 50%

<u>N</u>	<u>p1</u> 0.5	Reject first stage	0.14561	Power	85%
0	5.68E-14	16	0.0236875	32	0.0012
1	2.5E-12	17	0.0390147	33	0.00044
2	5.38E-11	18	0.058522	34	0.00014
3	7.53E-10	19	0.0800828	35	4E-05
4	7.72E-09	20	0.1001035	36	1E-05
5	6.17E-08	21	0.114404	37	2.2E-06
6	4.01E-07	22	0.1196042	38	4E-07
7	2.18E-06	23	0.114404	39	6.2E-08
8	1.01E-05	24	0.1001035	40	7.7E-09
9	4.03E-05	25	0.0800828	41	7.5E-10
10	0.000141	26	0.058522	42	5.4E-11
11	0.000436	27	0.0390147	43	2.5E-12
12	0.001199	28	0.0236875	44	5.7E-14
13	0.002951	29	0.013069		
14	0.006534	30	0.0065345		
15	0.013069	31	0.0029511		

23.3 Appendix C: Evidence of PD to Determine Trial Entry Eligibility

Patients being considered for trial entry should have evidence of disease progression by either PSA, modified RECIST or bone scan to be eligible.

PSA: PSA evidence of disease progression based on the prostate cancer working group (PCWG) 2 criteria consist of a minimum PSA level 2.0 ng/ml that has risen on at least 2 successive occasions, at least 1 weeks apart. The reference value # 1 is the last value before the rise in PSA was observed. If the confirmatory PSA value (Figure 5, # 3A) is greater than the screening value then progression by PSA is met and the patient is eligible for trial enrolment on the basis of PSA alone. If the confirmatory PSA (Figure 5, #3B) value is less than the screening PSA (Figure 5, #2) value, then an additional test for rising PSA (#4) will be required to document progression before the patient can be enrolled.

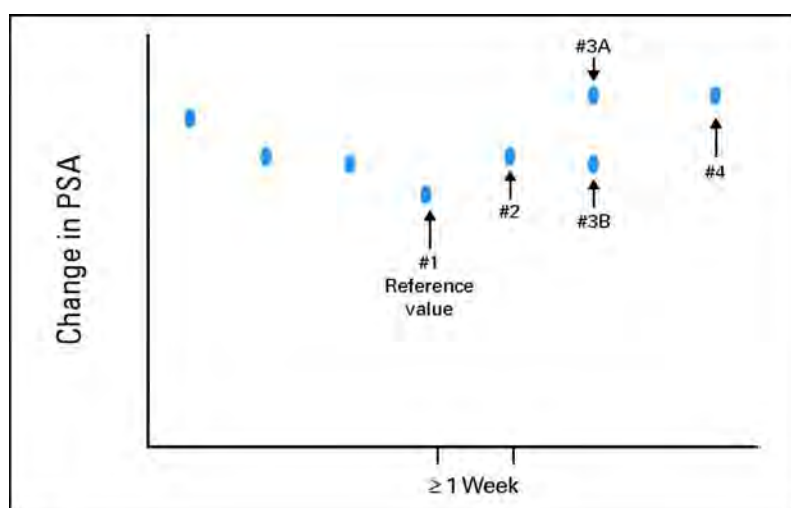


Figure 5: Eligibility Based on PSA

Target lesion/measurable disease: Patients are not required to have evidence of disease progression by measurable disease if they meet the criteria for disease progression on the basis of PSA or bone scan. Evidence of nodal or visceral disease RECIST progression however is sufficient for trial entry independent of PSA readings. Because lymph nodes may be enlarged due to benign pathology, only lymph nodes that are ≥ 2 cm should be used for disease evaluation.

Bone scan: Evidence of disease progression based on bone scan appearance is sufficient for trial entry independent of PSA readings. If the appearance of the bone scan is the only indicator of progression then there must be ≥ 2 new bone lesions compared with the prior bone scans. If there is ambiguity about the appearance of the bony lesions such as traumatic in nature or secondary to a flare reaction then it is recommended that an alternative imaging modality such as MRI or fine-cut CT be used to evaluate these lesions further.

23.4 Appendix D: Outcome Measures of Response / Progression Post Study Treatment

Procedures for Assessing PSA Response / Progression Post Study Treatment

PSA measurements will be done every 12 weeks on day1 of cycle 4,7,10 and every 3rd cycle thereafter. Increases and decreases will be tracked in order to assess disease response. The PSA readings on its own will not be used to define progression in this protocol. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG 2:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA from cycle1day1 (baseline) PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. The first PSA reading will be obtained at week 12.

Duration of PSA Response:

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the Cycle 1 Day 1 (baseline) value that has been confirmed by a second value until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be assessed at the last PSA measurement.

Time to PSA Progression:

For patients who have achieved a $\geq 50\%$ decrease from the Cycle 1 Day 1 (baseline), the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 4 or more weeks later. For patients without a PSA decrease of this magnitude or without a decrease, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented, which is confirmed by a second consecutive value 4 or more weeks later.

Procedures for Assessing Radiological Responses / Progression Post Study Treatment

Categorisation of response in this study will be based on modified RECIST 1.1 for soft tissue disease and appearance of bone scan for bone metastasis.

Bone metastasis evaluation:

The first bone scan should not be performed before 12 weeks post commencement of treatment unless clinically indicated as there may be evidence of a flare response early on which may confuse the response evaluation. A patient will be considered to have progressed on bone scan if the following criteria are met:

- If the first bone scan with 2 new lesions is observed ≤ 13 weeks from the point of Cycle 1 Day 1 and is confirmed by a follow up scan ≥ 6 weeks later showing 2 additional new lesions (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan).
- The first bone scan with ≥ 2 new lesions compared with baseline is observed > 13 weeks from Cycle 1 Day 1 and the new lesions are verified on the next bone scan ≥ 6 weeks later (i.e. a total of ≥ 2 new lesions compared with baseline). If the second scan confirms progression the data of the progression is the date of the first bone scan rather than the second confirmatory scan.

Measurable Disease Evaluation:

Changes in nodal and visceral disease should be recorded using the modified RECIST criteria defined in Appendix E.

Table 8: Radiological Criteria for Ascribing Disease Progression

Evidence of Progression	Confirmation	Action
Bone Disease Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment ≤ 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show an additional 2 new lesions compared to the first post treatment scan (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment > 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should confirm the presence of the 2 new lesions compared the baseline scan. (i.e. a total of ≥ 2 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Soft Tissue Disease as defined by RECIST on CT/MRI	Progression at any scheduled reassessment ≥ 12 weeks does not need to be confirmed.	Investigators are highly encouraged to maintain the patient's treatment with study medication unless radiological progression is observed.

Progression Free Survival (PFS)

In this protocol death, radiographic and unequivocal clinical progression comprise the PFS events. PFS is defined from the time of study entry to confirmed disease progression based on either:

- Radiological progression as documented on bone scans and / or measurable disease on CT scans

OR

- Unequivocal clinical progression

OR

- Death

The analysis of PFS is based on the time of the first progression observed. Where possible all disease assessment (Bone scan, CT, PSA) should be collected at the same time points.

23.5 Appendix E: Modified RECIST

The primary efficacy objective to this trial is based on tumour assessment. For the purpose of this study, definitions of soft tissue tumour assessments will be based on a Modified Response Evaluation Criteria in Solid Tumours 1.1 (RECIST1.1). Pertinent points are summarised below.

Evaluation of measurable and non-measurable lesions

1. **Measurable lesions** – lesions that can be accurately measured in at least one dimension with the longest diameter \geq 20 mm using conventional techniques or \geq 10 mm, with a spiral CT scan.
2. **Non-measurable lesions** – all other lesions, including small lesions (longest diameter \leq 10 mm, with a spiral CT scan), i.e., blastic bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
3. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, should not be included in assessment of response, but should be assessed for progression.
4. For this study, bone lesions are not considered “non-measurable” lesions for RECIST. Bone lesions will be assessed by bone scan only.
5. All measurements should be taken and recorded in metric notation, using a ruler or calipers. Preferably, all screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.
6. The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up.
7. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion is recommended.

Methods of measurement:

1. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.

2. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung, however CT scans are preferable.
3. Ultrasound (US), endoscopy and laparoscopy should not be used to measure tumour lesions. It is however a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound may also be used to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
4. Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions).

Baseline documentation of target and non-target lesions

1. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline and at the time points specified in the protocol.
2. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements.
3. A sum of the longest diameters (LD) for all target lesions will be calculated and reported as the baseline sum of LD. The baseline sum LD will be used as reference by which to characterise the objective tumour response.
4. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions will also be monitored throughout the study, and an overall assessment of response will be made. Details of any new lesions will also be recorded. It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Table 9: Response Criteria

Response criteria	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD)	At least 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	Whether sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Table 10: Responses in patients with both target and non-target disease

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/nonPD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD= progressive disease, NE= inevaluable

Table 11: Responses in patients with only non-target disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/nonPD	No	Non-CR/nonPD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD= progressive disease, NE= inevaluable

Reproduced from: <http://www.recist.com/recist-comparative/01.html> and Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 12 weeks) that is defined in the study protocol.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

23.6 Appendix F: ECOG Performance Status

Table 12: ECOG Performance Status

ECOG Performance Status	Function
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead


23.7 Appendix G: National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.02)

V4.02 (CTCAE): publish date August 9, 2010:
ctep.cancer.gov/reporting/ctc.html

23.8 Appendix H: World Medical Association Declaration of Helsinki

<http://www.wma.net/e/policy/b3.html>

23.9 Appendix I: Brief Pain Inventory (Short Form)


 Date: / /
(month) (day) (year)

Study Name: _____
 Protocol #: _____
 PI: _____
 Revision: 07/01/05

Subject's Initials: _____
 Study Subject #:

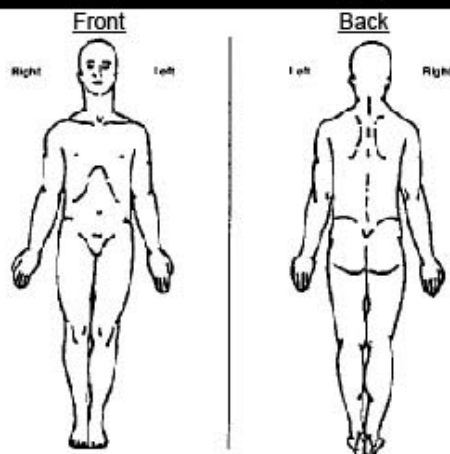
PLEASE USE BLACK INK PEN

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the **average**.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

23.10 Appendix J: Total blood volumes drawn at each time point

Study time points	Months on study	Total volume of safety and research bloods per month
Screening	-1	92.5mls (102.5mls)*
Cycle 1 Day 1	1	156.5 mls (166.5mls)*
Cycle 1 Day 8		
Cycle 1 Day 15		
Cycle 2 Day 1	2	74mls
Cycle 3 Day 1	3	76.5mls
Cycle 4 Day 1	4	38mls
Cycle 5 Day 1	5	44.5mls
Cycle 6 Day 1	6	24mls
Cycle 7 Day 1	7	38mls
Cycle 8 Day 1	8	12mls
Cycle 9 Day 1	9	12mls
Cycle 10 Day 1	10	38mls
Cycle 11 Day 1	11	12mls
Cycle 12 Day 1	12	12mls
End of study		92.5mls
*Patients treated at the Royal Marsden Hospital will have an additional 10 ml sample of blood obtained at Screening and Cycle 1 Day 1		

TOPARP

Phase II Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer

Chief Investigator	Prof. Johann de Bono
Co-Sponsors:	The Royal Marsden Hospital NHS Foundation Trust / The Institute of Cancer Research
Approval:	Cancer Research UK Clinical Trials Awards & Advisory Committee (CTAAC) and Biomarkers Imaging Development and Discovery Committee (BIDD)
Funders:	Cancer Research UK AstraZeneca
Coordinating Trials Unit:	Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU)

PROTOCOL Version 3.0 22nd November 2012

EudraCT Number: 2011-000601-49	CTA Number: 22138/0016/001-0001
ICR-CTSU Protocol Number: ICR-CTSU/2011/10030	ICR/RMH CCR Number: 3592
Main REC Reference Number: 11/LO/2019	ISRCTN: 15124653
CR UK Reference Number: CRUK/C12540/A12354	

The TOPARP trial is part of the National Institute for
Health Research Clinical Research Network Trial Portfolio



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The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group and Principal Investigators from a subset of participating centres. A copy of the current membership of the TMG can be obtained from the TOPARP Trial Manager at ICR-CTSU.

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This protocol describes the TOPARP trial and provides information about procedures for entering patients. The protocol should not be used as a guide for the treatment of other patients. Every care has been taken in the preparation of this protocol, however corrections or amendments may be necessary. These will be circulated to investigators in the trial. Centres entering patients for the first time are advised to contact ICR-CTSU to confirm they

have the most recent version. Protocol amendments will be circulated to participating centres as they occur.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended. It will be conducted in compliance with the protocol, the Data Protection Act (Z6364106) and other regulatory requirements as appropriate.

Glossary of Abbreviations and Definitions of Terms

AD	Androgen deprivation
ADP	Adenosine diphosphate
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase (SGPT)
APTT	Activated partial thromboplastin time
AST	Aspartate Transaminase (SGOT)
AR	Androgen receptor
AZ	AstraZeneca
BID	Twice daily
BER	Base excision repair
BP	Blood Pressure
BUN	Blood urea nitrogen
°C	Degrees Celsius
FBC	Full Blood Count
cm	Centimetre
CR	Complete Response
CrCl	Creatinine clearance
CRF	Case Report Form
eCRF	Electronic Case Report Form
CRPC	Castration Resistant Prostate Cancer
CT	Computerised Tomography
CTC	Circulating Tumour Cell
CTCAE	Common Terminology Criteria for Adverse Events
D	Day (as in treatment day)
dL	Decilitres
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DRE	Digital rectal exam
DSB	Double Strand Breaks
DW-MRI	Diffusion-weighted MRI
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
FDA	Food and Drug Administration
FISH	Fluorescent in-situ hybridisation
FBC	Full Blood Count
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyltransferase
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
Ha	Alternative Hypothesis
H2AX	Histone H2AX
Ho	Null hypothesis
HR	Homologous Recombination
IB	Investigator Brochure
IC50	Dose for 50% inhibition
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IF	Immunofluorescence
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRB	Institutional Review Board
ITT	Intention To Treat
kg	Kilogram
LD	Longest Diameter
LDH	Lactic Dehydrogenase
LHRH	Luteinizing Hormone Releasing Hormone
mg	Milligram
MRI	Magnetic Resonance Imaging
miRNAs	MicroRNAs
NAD	Nicotine adenine dinucleotide
NCI	National Cancer Institute
NCICTC	National Cancer Institute Common Terminology Criteria
nM	Nanomolar
NRS	Numeric Rating Scale
ORR	Overall Response Rate
PARP	Poly (ADP-ribose) polymerase
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD	Pharmacodynamic
PFS	Progression Free Survival
PICF	Patient Informed Consent Form
PIN	Prostatic Intraepithelial Neoplasm
PK	Pharmacokinetic
PO	Per Oral (by mouth)
PR	Partial Response
PSA	Prostatic Specific Antigen
PCWG2	Prostate Cancer Working Group 2
PT	Preferred Term
PTEN	Phosphatase and Tensin Homologue
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SD	Stable disease
SUSAR	Serious unexpected suspected adverse (drug) reaction
SBP	Systolic blood pressure
SSB	Single Strand Break
SOC	System Organ Class
μM	Micromolar
ULN	Upper Limit of Normal
UA	Urinalysis
WBC	White Blood Cells

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1 TRIAL SUMMARY

PROTOCOL TITLE	Phase II Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer (TOPARP).
TARGET DISEASE	Castration resistant prostate cancer (CRPC)
STUDY OBJECTIVES	<ul style="list-style-type: none"> To evaluate the anti-tumour activity of olaparib in metastatic castration resistant prostate cancer To identify molecular signatures of tumour cells in responding and non-responding patients To clinically qualify putative predictive biomarkers of PARP inhibitor sensitivity
STUDY DESIGN	Open-label, single arm, two part adaptive design phase II trial.
TRIAL POPULATION	Patients with an advanced CRPC who have failed androgen deprivation and taxane-based treatment.
TREATMENT REGIMEN	Patients will receive single agent olaparib 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.
RECRUITMENT TARGET	Part A: between 30-45 patients Part B: 44 patients
PRIMARY ENDPOINT	Response will be defined on the basis of the following outcomes, if any of these occur patients will be considered to have responded: <ul style="list-style-type: none"> Objective response by modified RECIST PSA decline of $\geq 50\%$ according to the Prostate Cancer Working Group 2 (PCWG2) Conversion of circulating tumour cell count (CTC) from ≥ 5 cells/7.5 ml blood at baseline to < 5 cells/7.5 ml confirmed by at least two readings 4 weeks apart
SECONDARY ENDPOINTS	<ul style="list-style-type: none"> Radiological progression free survival Time to radiological progression Progression free survival Overall survival Time to PSA progression Proportion of patients with conversion of CTC count from $\geq 5/7.5$ ml blood at baseline to $< 5/7.5$ ml blood nadir Duration of PSA response and objective response (PSA-ORR), if applicable Safety and tolerability of olaparib
EXPLORATORY ENDPOINTS	<ul style="list-style-type: none"> To evaluate the impact of treatment with olaparib on bone metastasis imaging by DW-MRI in selected patients and to correlate these results with PSA, CTC and radiological responses

	<p>by conventional imaging.</p> <ul style="list-style-type: none"> • To determine the proportion of patients achieving pain improvement with olaparib treatment.
<p>TRIAL OUTLINE</p>	<ul style="list-style-type: none"> • There will be screening period of up to 28 days prior to cycle 1 day 1. • Archival tissue is mandated for enrolment into the study. Patients who do not have a prior histological diagnosis or archival tissue available will be required to have a tumour biopsy. PART A of the study will be open to all comers. In PART B the tumour tissue of the patients being considered for enrolment will be analysed first to ensure the presence of the putative predictive biomarkers and only patients with the predictive biomarkers will be enrolled. • Patients will receive single agent 400mg of olaparib, twice daily, continuously on 28-day cycles. • During the study period, no other anticancer or hormonal treatment will be given although a LHRH analogue must be continued, unless the patient is surgically castrate. <p>Efficacy Assessments:</p> <ul style="list-style-type: none"> • Baseline CT scans, bone scan and DW-MRI (optional) will be performed as close as possible to cycle 1 day 1 of treatment. These scans will be repeated after every 3 cycles (12 weeks) or earlier if clinically indicated. • PSA will be assessed at baseline and every 12 weeks by PCWG2 criteria. In the absence of radiological disease progression patients should continue on study. <p>Safety Assessments:</p> <p>Safety parameters will be continuously assessed throughout the study prior to each cycle of treatment. Adverse events (AEs) and serious adverse events (SAEs) including laboratory tests will be graded and summarised according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events version 4.02 (CTCAE v4.02).</p> <p>Based on Phase I and Phase II studies, olaparib is generally well tolerated. Safety concerns are mainly related to the possibility of myelosuppression. Patients who experience a NCI-CTCAE grade 3-4 haematological or non-haematological toxicity that the investigator attributes to olaparib may have an interruption of olaparib treatment for up to 42 days until recovery of all toxicities to no more than NCI-CTCAE grade 1. Those patients on continuous treatment requiring a delay in dosing by >14 days will require a dose reduction to 300mg BID. If the adverse event recurs at the same severity, treatment can be interrupted again and on resolution to ≤ NCI-CTCAE grade 1 toxicity a further dose reduction to 200 mg BID can be made. If the adverse event recurs despite the second dose reduction a final dose</p>

	<p>reduction to 100mg BD is permitted.</p> <p>Olaparib should be withheld in the event of:</p> <ul style="list-style-type: none"> • Grade 4 neutropenia • Grade 2-4 neutropenia with infection • Platelet count lower than $50 \times 10^9/L$ • Non-haematological toxicity grade 3 or greater, except nausea, vomiting or diarrhoea and fatigue associated with suboptimal pre-medication and/or management OR transient and clinically insignificant biochemical blood results. • Aspartate transaminase (AST) or alanine transaminase (ALT) elevations grade 3 or higher for more than 7 days. • Any other toxicity that, in the view of the principal investigator and the medical monitor, represents a clinically significant hazard to the patient until resolution of toxicity to no more than grade 1. <p>Biomarker Assessments:</p> <p>All patients enrolled in the study are required to have archival tumour tissue, fresh tumour biopsies, blood and urine samples collected during the study for the purpose of biomarker analyses including the following:</p> <ul style="list-style-type: none"> • Circulating tumour cells (CTCs): enumeration & molecular characterisation • PTEN and ERG immunohistochemistry (IHC) on primary tumour tissue and fresh paired biopsies • PTEN and ERG immunofluorescence (IF) in CTCs • <i>TMPRSS2-ERG</i> and <i>PTEN</i> fluorescence in situ hybridisation (FISH) studies in primary tumour, paired biopsies and CTCs • γH2AX and RAD51 foci formation in paired tumour biopsies and CTCs • Markers of tumour cell proliferation and cell cycle phase in paired tumour biopsies and CTCs • Circulating plasma tumour DNA • Circulating plasma tumour and whole blood RNA • Urine telopeptides and RNA • Proteomic profile • Metabolomics profile
<p>FOLLOW UP</p>	<p>Patients will be treated until disease progression (radiological progression) or withdrawal from the study for another reason. After discontinuing study treatment patients will be reviewed 30 +/- 5 days post cessation of treatment for an end of treatment safety assessment and 3 monthly for survival data.</p>

2. INTRODUCTION

2.1 Metastatic Castration Resistant Prostate Cancer

Prostate cancer is the second leading cause of male cancer-related mortality in the United Kingdom (1). While a proportion of patients have indolent disease, curable with local treatment, approximately a third of patients fail local treatment and develop incurable metastatic disease. Androgen deprivation therapy constitutes the mainstay of treatment for advanced prostate cancer. Most patients with advanced disease initially respond to hormonal deprivation therapy; however resistance inevitably develops within 1-3 years and represents a transition to more aggressive and invariably fatal disease. Recent studies have established that androgen signalling continues to play a pivotal role in tumour progression as castration resistance evolves. Androgen receptor (AR) gene amplification, AR overexpression, AR activating mutations and the presence of sufficient intratumoural androgen levels contribute to continued AR signalling despite a systemic castrate state. The recent emergence of the CYP17 inhibitor, abiraterone and other novel antiandrogens such as MDV3100 provide clinical validation that targeting AR signalling remains a useful approach in a significant proportion of CRPC patients (2, 3).

Metastatic prostate cancer is often associated with significant disease-related morbidity. The vast majority of these patients develop bone metastasis with clinical sequelae of bone pain, skeletal fractures, spinal cord compression and haematological compromise. In addition, soft tissue disease is liable to cause urinary obstructions and other problems.

Most CRPC patients have received multiple lines of hormonal manipulation prior to commencing chemotherapy for ongoing disease progression. Docetaxel and more recently cabazitaxel, Sipuleucel-T, alpharadin and abiraterone have demonstrated an overall survival advantage for metastatic CRPC (mCRPC) albeit of only several months (2, 4, 5, 6). Despite these important incremental advances in treatment options, benefits remain modest and the median survival of patients with mCRPC is unsatisfactory at approximately 18 – 36 months. It is clear that there is an urgent need for better treatments that offer durable clinical benefit and further improvement in overall survival for these patients.

Platinum Based Second-line Chemotherapy in Patients with CRPC

Platinum-based chemotherapy in Phase II trials has provided encouraging response rates (PSA and radiological) in the range of 44-60% and a median progression free survival (PFS) of 4-9.5 months in the post-docetaxel CRPC setting (7, 8). Likewise, satraplatin, an orally bioavailable platinum compound, has shown second-line antitumour activity in unselected patients in a Phase III trial, with a 50% PSA decline rate of 33% and a statistically significant PFS advantage in 40% of the patients (9). The lack of survival outcome in this study, despite the anti-tumour activity observed, may in part relate to inter-patient molecular heterogeneity and failure to optimally select the subgroup of tumours most likely to respond to this strategy.

Platinum salts induce interstrand and intrastrand DNA cross-links and consequently increased levels of double-strand (ds) DNA damage. Platinum compounds and PARP inhibitors (PARPi) exert their anti-tumour activity in a similar way by inducing increased ds-DNA breaks which overwhelms the DNA repair machinery in homologous recombination (HR) repair deficient tumours, consequently resulting in tumour cell death. Tumour sensitivity to the Poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib has been shown to correlate with prior platinum sensitivity in HR deficient, *BRCA1/2* mutant cancers (10, 11). It follows therefore that the previously established antitumour activity for satraplatin in prostate cancer supports the widely held premise that there is indeed a subgroup of CRPC that harbour HR DNA repair defects and will benefit from treatment with the PARP inhibitor, olaparib. No platinum is currently approved for the treatment of CRPC; indeed most CRPC remain platinum naïve. Recruitment of patients most likely to benefit based on biomarker driven molecular sub-classification is critically important for the successful development of novel therapies such as olaparib in this disease.

Prostate Cancer Heterogeneity: Clinical and Molecular

Prostate cancer is a highly heterogeneous disease with patients responding differently to treatments and overall having very different clinical outcomes. This is also reflected at a molecular level (12-16). Different molecular variants portend different clinical outcomes possibly secondary to distinct differences in molecular drivers. Despite this, to date, Phase III trials of novel anticancer drugs in this disease have failed to stratify patients on the basis of molecular profile and likely benefit. This inter-patient molecular heterogeneity may, in part, account for the high risk of failure of pivotal Phase III trials of anticancer drugs in this disease. We envision that an improved understanding of the biological and clinical significance of the molecular sub-classification of this disease will positively impact pivotal randomised clinical trials in this disease. The identification of primary tumour prognostic and predictive molecular markers as compared to the currently utilised suboptimal clinicopathological parameters will allow improved patient selection for optimal CRPC treatments thus maximising clinical benefit while avoiding unnecessarily exposure and toxicity in patients unlikely to benefit.

Dissecting Prostate Cancer Heterogeneity by FISH: *PTEN* & *ETS* Gene Rearrangements.

Functional Loss of *PTEN*

Prostate cancer can be molecularly sub-classified using multi-colour fluorescent in situ hybridisation (FISH). Dissecting the molecular profile of prostate cancers in this way has resulted in the characterisation of multiple commonly occurring genetic aberrations implicated in promoting tumour genesis (12, 15, 17, 18). The biological significance of gene rearrangements, deletions and amplifications as well as possible predictive and prognostic relevance are currently being extensively studied. Phosphatase and tensin homologue (*PTEN*), a tumour suppressor gene, negatively modulates the phosphatidylinositol 3-kinase (PI3)/AKT signal transduction pathway which fosters tumour growth, proliferation and survival (19-22). Bi-allelic and mono-allelic deletion of *PTEN* is a common event in prostate cancer and is implicated in tumour pathogenesis and progression (22-25). *PTEN* functional loss is associated with more advanced disease, higher-grade tumours and a worse clinical

outcome (15, 24-27). The frequency of reported *PTEN* inactivation in prostate cancer is variable in the literature, with mono-allelic and bi-allelic loss by FISH in the range of 30-68% (23, 26, 27, 28). Our own analysis has shown a complete loss of *PTEN* expression by immunohistochemistry (IHC) in archival tissue in approximately 50% in patients on the abiraterone phase I-II studies. The variability seen in the literature may be related to tumour stage, tissue processing, and IHC methodology. A recent study of tumour material from 59 patients with CRPC revealed that the *PTEN* gene was deleted in 77% of cases; 25% with homozygous deletions, 18% with homozygous and hemizygous deletions and 34% with hemizygous deletions. Bi-allelic *PTEN* loss was correlated with disease-specific mortality in this study (24).

Evidence for the importance of *PTEN* functional loss in prostate carcinogenesis also comes from transgenic studies. Critically, conditional *PTEN* loss in prostates from transgenic mice leads to the late development of metastatic prostate cancer (29). Prostate restricted overexpression and activation of AKT, however, resulted only in prostatic intraepithelial neoplasia (PIN) formation (30). These data suggest that *PTEN* loss may possibly induce prostate carcinogenesis not only through its phosphatase PI3K/AKT regulatory role but also possibly through its nuclear, DNA repair, role that has been recently reported (31, 32).

***TMPRSS2* Chromosomal Translocation**

Chromosomal translocation involving the androgen-responsive gene transmembrane protease serine 2 (*TMPRSS2*) with the oncogenic erythroblast transformation specific (*ETS*) transcription factor family of genes (*ETV1*, *ETV4*, *ETV5*) is reported in 50%-70% of prostate cancers (17, 33). *TMPRSS2/ERG* is the predominant type of gene fusion seen and results in overexpression of 3'-*ERG* sequence joined to the 5'-*TMPRSS2* promoter. Less frequently *TMPRSS2* becomes fused to *ETV1* and *ETV4*. *ERG* and other *ETS* family members are transcription factors that are implicated in the control of cell growth and differentiation. *TMPRSS2/ERG* fusion rearrangement has been shown to co-operate with *PTEN* haploinsufficiency to promote carcinogenesis (17, 22, 34) and accounts for continued hormone driven disease (35). Recent evidence implicates topoisomerase IIB-mediated DNA breakage during the induction of transcriptional programs in generating these *TMPRSS2/ERG* fusion rearrangements (36, 37, 38).

We have utilised validated FISH assays to evaluate *PTEN* deletions and the commonest *ETS* gene rearrangements (*ERG* and *ETV1*) on the Trans-Atlantic Prostate Group (TAPG) tissue microarray (TMA) (15). We demonstrated that patients with *PTEN* loss (heterozygous or homozygous: 17% of newly diagnosed cancers) had significantly worse cause-specific and overall survival compared with patients with no *PTEN* loss, supporting the haploinsufficiency proposed for the *PTEN* gene (Figure 1). Three hundred and eight patients with both *ETS* gene (*ERG* and *ETV-1*) rearrangement and *PTEN* loss status available were analysed for survival outcome (Figure 2). The largest group of patients (n=167, 54%) had no *ERG* or *ETV-1*-gene rearrangement and no *PTEN* loss and had the best outcome with 85.5% survival at 11 years. A poor prognosis group was also identified (n=19, 6%) who had *PTEN* loss but no *ERG* or *ETV-1*-gene rearrangement with a cause-specific survival of 13.7% at 11 years and a median survival of 5 years from diagnosis. Patients with an *ETS* gene rearrangement with or without *PTEN* loss had an intermediate prognosis in keeping with the hormonal sensitivity of these cancers, which has recently

been described (15, 27). Overall, therefore, these data indicate that prostate cancer is a molecularly heterogeneous disease, with cancers demonstrating PTEN loss having a poor outcome, and that to accelerate the successful development of targeted therapies in CRPC, identifying the appropriate subgroup of patients most likely to benefit is paramount.

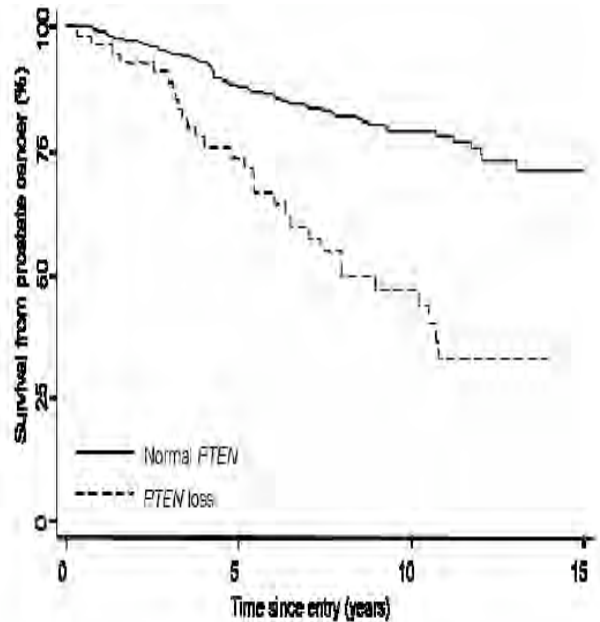


Figure 1: PTEN loss prostate cancers have a worse overall survival

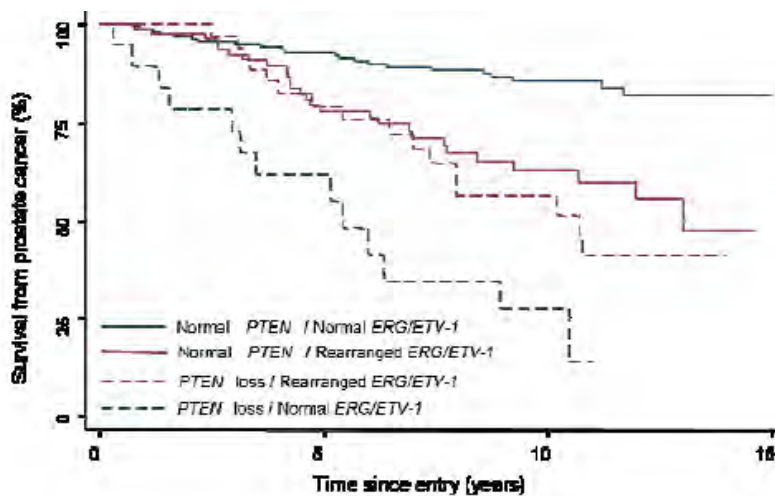


Figure 2: Multi-colour FISH based stratification by studying *ETS* rearrangements and PTEN loss.

PTEN Loss, *ETS* Gene Rearrangements and HR Repair Defects

PTEN is implicated in many functions, both PI3K/AKT dependent and independent. Recent reports suggest in addition to lipid phosphatase function, PTEN localises to the nucleus and that its function includes maintenance of genomic stability (31, 32) by a number of mechanisms including interacting with CENP-C an integral centromeric binding and

stabilising protein, regulating the transcription of RAD51, a critical DNA double strand break (DSB) repair protein (39) and modulating cell cycle progression (40).

PTEN loss results in impaired HR DNA repair with reduced RAD51 expression, increased chromosomal aberrations and genomic instability (31,39). Moreover, in vitro cell-based experiments and in vivo xenograft studies have established that PTEN deficient tumour cells much like *BRCA1/2* deficient tumours are selectively sensitive to platinum compounds and potent PARP inhibitors including olaparib (41-43). Furthermore, restoration of PTEN expression in PTEN deficient tumour cell lines restores PARP inhibitor resistance, confirming PTEN as a determinant of the response to PARP inhibition. This synthetic lethal relationship between PTEN-null tumours and PARP inhibition supports the therapeutic utility of PARP inhibitors in PTEN-deficient tumours. Moreover, *ERG*, the oncogene driven by the commonest prostate cancer genetic driver lesion *TMPRSS2/ERG*, has been shown to directly associate with PARP and requires PARP for its transcriptional regulatory function with PARP inhibition having antitumour activity in *ERG* rearranged tumour models (44,45).

Given these pre-clinical observations and the putative role of PTEN in maintaining chromosomal stability, we predict that tumours with PTEN loss and /or *ETS* gene rearrangements are likely to be hypersensitive to PARP inhibition. We therefore aim to evaluate the antitumour activity of olaparib in patients with sporadic CRPC using an adaptive biomarker driven design to identify and clinically qualify predictive biomarkers of olaparib sensitivity for optimal patient selection.

2.2 PARP and PARP Inhibition

Poly(ADP-ribose) polymerase 1 (PARP-1) is a zinc-finger DNA-binding enzyme that is activated >500 fold upon binding to DNA double or single strand breaks (46). PARP-1 (113 kDa) and PARP-2 (62 kDa) are thus far the only members of the PARP enzyme family known to be involved in DNA damage signalling and repair with a degree of functional redundancy between these proteins. PARP-1 signals the presence of DNA damage and plays a critical regulatory role in DNA damage repair. PARP-1 is involved in a wide range of cellular processes including DNA repair and maintenance of genomic integrity, regulation of protein expression at the transcriptional level, regulation of cellular replication and differentiation, regulation of telomerase activity, and involvement in the cell apoptotic pathway (47).

PARP-1 comprises 3 domains, the N-terminal DNA-binding domain containing 2 zinc fingers, the auto-modification domain and the C-terminal catalytic domain. PARP-1 binds to both single and double-stranded DNA breaks through the zinc-finger domain and catalyses the cleavage of nicotinamide adenine dinucleotide (NAD)⁺ into nicotinamide and ADP-ribose, and subsequently transfers successive units of ADP-ribose onto DNA, histones, PARP-1 and other DNA repair proteins to form branched ADP-ribose polymers. These branched ADP-ribose polymers result in post-translational modification of histones and other nuclear proteins which convert the DNA damage signal into intracellular signals that activate either DNA base-excision-repair (BER) pathways or cell death if the damage is beyond repair. Other transcriptional factors and signalling molecules are also poly-ADP-

ribosylated by PARP-1 to initiate a multitude of other important cellular functions (47,48). Given the critical role that PARP plays in single strand DNA repair it is not surprising that PARPi are able to potentiate the cytotoxic damage incurred with DNA-damaging chemotherapy agents and ionizing radiation (49). PARP inhibitors have also shown significant single agent activity in tumours with HR deficiency (10,11, 50,51).

Synthetic Lethality Between *BRCA1/2*-mediated Homologous Recombination Repair and PARP-1

Abrogating PARP dependent BER, which is responsible for repairing DNA single strand breaks (SSBs) results in the accumulation of SSBs. These SSBs collapse at the replication forks during DNA synthesis giving rise to double strand breaks (DSBs) that are detrimental to the cell. The DNA DSBs are preferentially repaired by high fidelity HR repair that restore genomic integrity under normal circumstances. *BRCA1* and *BRCA2* genes encode proteins that are essential in HR repair. *BRCA1/2* deficient tumour cells lack HR repair capacity and are therefore unable to repair these replication associated DSB DNA damage, which accumulates in the context of suppressed PARP activity, leading to chromosomal instability, cell cycle arrest and apoptosis. The profound selective sensitivity of *BRCA* deficient tumour cells for PARPi compared with unaffected heterozygous mutant normal tissue retaining one functional *BRCA* allele provides a large therapeutic window (47,52,53).

Preclinical models have demonstrated that HR deficient tumour cells with *BRCA1*^{-/-} and *BRCA2*^{-/-} genotype are exquisitely sensitive to PARP inhibition with olaparib (previously referred to as KU-0059436 or AZD2281 in earlier studies), in contrast to heterozygous mutant or wild-type cells (52). Likewise, in the clinic, olaparib is an efficacious therapy with durable antitumour activity and a favourable toxicity profile in HR deficient tumours arising in *BRCA1* and *BRCA2* mutation carriers including several patients with mCRPC (11).

Epigenetic Disruption of *BRCA 1/2* Function and Other Causes of HR Impairment

It has been hypothesised that targeting SSB DNA repair with PARPi will be a useful therapeutic strategy in sporadic tumours that harbour HR repair defects. This may occur due to either epigenetic or genetic silencing of *BRCA1/2* function or disruption of any of the other key proteins that make up the HR repair pathway. Loss of *BRCA 1/2* function may arise spontaneously via somatic mutations and epigenetic mechanisms during tumour formation. These somatic mechanisms of *BRCA1/2* functional loss are increasingly implicated in sporadic carcinogenesis (54,55). Epigenetic gene silencing of tumour-suppressor genes is a well-recognised phenomenon with methylation of the *BRCA1* promoter found in 11-14% of sporadic breast cancers and 5-31% of ovarian cancers (56). Epigenetic modification of the Fanconi anaemia/*BRCA* pathway through promoter hypermethylation in lung, oral cancer and cervical cancer cell lines render these cells highly sensitive to DNA cross-linking agents (57,58). Somatic mutations of *BRCA* genes and heterozygous loss also appear to be more common than previously defined (54,58,59). The term “BRCAness” is commonly used to describe the phenotypic likeness of a sporadic tumour with a familial-*BRCA1/2* mutation related cancer (56). Identification of this BRCAness phenotype secondary to epigenetic / genetic silencing of the Fanconi anaemia/*BRCA* pathway may select for clinical benefit from PARPi in these sporadic cancers.

In addition to somatic *BRCA1/2* dysfunction, disruption of any of the other critical proteins that make up the HR repair pathway such as RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHEK1, CHEK2, FANCD2, FANCA or FANCC 2 have been shown in preclinical models to cause HR deficiency and render these tumour cells highly susceptible to synthetic lethality with PARPi (56, 60, 61).

Clinical evidence supporting single agent olaparib antitumour activity in sporadic cancer was recently reported (58,62,63), with durable objective responses observed in 28% of sporadic high grade serous ovarian cancers in one study and a further study reporting a significant improvement in progression free survival (62,63). These responses may be explained in part by the high frequency of somatic mutations of *BRCA1/2* as well as epigenetic silencing of this and other key HR genes in high grade serous ovarian cancer (58). These results have led to the further evaluation of single agent olaparib in other tumour types enriched for HR defects. Identifying the subgroup of sporadic tumours with HR defects through validated predictive biomarker studies is imperative, if we are to successfully develop novel treatments such as PARP inhibitors (PARPi) and personalise medicine.

There has been limited investigation to date of the incidence of somatic aberrations in key HR related genes in advanced prostate cancer. High penetrance germline mutations in several candidate genes involved in DSB repair including *BRCA1*, *BRCA2*, *CHEK2*, *BRIPI/FANCI* and *NBS1* are known to account for a small fraction of prostate cancer cases (64-70). *PTEN* however is one of the commonest tumours suppressor genes that is deregulated in prostate cancer and is implicated in the pathogenesis of this tumour as discussed above. Loss of *PTEN* function may also result in deficient HR DNA repair with reduced RAD51 expression and sensitivity to PARP inhibition (39,41). Likewise, the *ERG/TMPRSS2* gene rearrangement which is observed in 50% of prostate cancers is also implicated in conferring sensitivity to PARPi (44). Overall, these data support the evaluation of PARP inhibitors in the treatment of advanced prostate cancer.

2.3 Rationale for Study

Despite recent advances in CRPC treatment, metastatic prostate cancer remains a common disease with a poor outlook. Improved treatments that offer durable clinical benefit and significant survival impact remain an area of unmet medical need. As with most chemotherapies, a proportion of prostate cancers will not respond due to the underlying tumour biology and inherent resistance mechanisms. Understanding the underlying molecular determinants of response and resistance to different treatments is critical for improvement in CRPC patient outcome through optimally selected treatments.

The previously established antitumour activity of platinum based regimens in advanced prostate cancer suggests that there is a subgroup of CRPC susceptible to DNA damaging agents such as platinum and PARPi.

The PARP inhibitor, olaparib is a novel anticancer agent with strong preclinical and clinical data for significant antitumour activity in HR repair deficient tumours arising in *BRCA1* and *BRCA2* mutation carriers including a number of patients with metastatic CRPC

(10,11,50,51,52,53). Recent clinical evidence supports the utility of this approach in sporadic high-grade ovarian cancers enriched for HR defects (62,63). Moreover, there is a growing body of preclinical evidence that supports extending this approach to a wide range of other sporadic tumours with disruption to other non-redundant components of the HR repair pathway including RAD51 and other essential HR repair proteins (60,61). Identifying these sporadic tumours with HR repair defects through validated predictive biomarkers remains a challenge and focus of ongoing research.

PTEN loss has been implicated to confer HR DNA repair defects with reduced RAD51 expression, increased genomic instability and tumour sensitisation to PARP inhibition (41-43). Homozygous *PTEN* loss by FISH is present in 20-30% of CRPC, with loss of protein expression by IHC being far more common (21). In addition, the *TMPRSS2/ERG* driver rearrangement, which is present in approximately 50-60% of prostate cancers and co-associates with *PTEN* loss has also been reported to confer sensitivity to PARP inhibition (44,45).

The target population for this trial are patients with advanced metastatic CRPC progressing following docetaxel treatment. A proportion of patients may also have received treatment with abiraterone and cabazitaxel. Given the high prevalence of loss of *PTEN* function and *TMPRSS2/ERG* rearrangements in this population and the strong preclinical rationale for this therapeutic strategy, we anticipate that a subgroup of these patients will benefit from olaparib treatment.

Patients may continue olaparib treatment until disease progression or treatment intolerance. Patients may however withdraw from the study at any point if they choose to do so or if the investigator believes it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for reducing the dose of olaparib are provided.

Rationale for Circulating Tumour Cell Based Studies in CRPC

Enumeration of circulating tumour cells (CTC) number using the Cell Search system (Veridex, PA) is a valid biomarker to monitor the effectiveness of therapy of patients with metastatic breast cancer (71-73), colorectal cancer (74) and prostate cancer (75-78). High baseline counts have consistently been associated with more aggressive disease and a worse outcome (76-78). CTC counts are highly prognostic for overall survival, and CTC count falls post-treatment associate with an improved overall survival and response to therapy in CRPC. In a pilot study, univariate analysis demonstrated that CTC counts of $< 5/7.5$ ml blood or $\geq 5/7.5$ ml blood correlated with OS (0.002; HR=7.37); in multivariate analyses CTC counts and PSA doubling time were the only 2 independent predictors of outcome unlike PSA, Gleason score, presence and absence of bony metastasis and age (75). In a similar study that related changes in CTC counts in patients with CRPC during the first 2 cycles of treatment with clinical outcome, we observed that patients with CTC counts that remained below 5 cells/7.5 ml blood during treatment with cytotoxic therapy had the best outcomes, whilst patients whose counts changed from $\geq 5/7.5$ ml blood to ≤ 5 had improved outcomes compared to the patient cohort whose CTC count remained persistently elevated at $\geq 5/7.5$ ml blood throughout treatment. In addition, patients whose CTC counts

increased during treatment from < 5 to $\geq 5/7.5$ ml blood had a similar poor outcome to the group whose count remained persistently elevated at ≥ 5 CTCs throughout treatment suggesting the development of treatment resistance (76). CTC counts were commonly detected in patients with advanced CRPC; CTC counts $>5/7.5$ ml were detected in 19/49 (39%) and 21/28 (75%) of chemotherapy –naïve and post–docetaxel patients respectively treated on the phase I-II Abiraterone studies (35). We now have data from almost a thousand patients participating in the randomised Phase III abiraterone trial (COU-301) that CTC conversion from ≥ 5 to <5 as well as any fall in CTC from 10% to 90% count post-treatment at 1, 2, 3 months after starting abiraterone is a statistically robust surrogate/intermediate endpoint of overall survival, meeting all of Prentice's criteria for surrogacy (78)

In addition, CTCs have been shown to retain many of the genomic characteristics of the primary tumour and thus provide a useful opportunity to study molecular changes in the disease profile longitudinally with ongoing treatment. Multicoloured FISH assays have been successfully applied to determine commonly found genomic alterations such as AR amplification, *PTEN* deletions and *TMPRSS2/ERG* fusion rearrangements in prostate CTCs (35,79,80). We have also developed multiplex immunofluorescence assays to evaluate protein expression in CTCs.

Rationale for Radiographic PFS and 6 months PFS as an Endpoint

Clinical research in prostate cancer has been hindered by the difficulty in objectively defining cancer progression. Composite endpoints that include patient reported, radiographic, and skeletal-related events have suffered from subjectivity. Conventional RECIST alone has limitations in CRPC in defining radiographic progression due to the fact that fewer than 50% of men with CRPC have measurable lesions greater than 2cm in size, and most of these lesions are in lymph nodes which impact survival less than visceral metastases (81). Conventional RECIST also lacks the sensitivity to differentiate true progression of bone metastasis from the flare phenomenon on bone scan or CT scan due to healing of previous bone metastasis (82,83). Although radiographic PFS is not a surrogate for overall survival in patients receiving docetaxel therapy, it outperforms PSA based progression (83).

Attribution of disease progression due to tumour flare phenomenon will be mitigated in this study by applying the new consensus guidelines that requires a confirmatory bone scan at least six weeks after the original scan to define progression. This will reduce the number of false positive determinations of CRPC progression. (Refer to Appendix D)

Progression of metastatic bone disease is of paramount importance to CRPC patients since it is responsible for severe morbidity of skeletal related events such as fracture, pain, and spinal cord compression. Similarly, progression of soft tissue metastasis may be associated with clinically significant morbidity. Prevention or delay in cancer progression should result in clear clinical benefit to the patient. In conclusion, radiologic PFS (rPFS) is an objective measurement that may associate with clinical benefit in the proposed study population.

Pain and Analgesic Assessments

Pain due to bone metastases and nerve root compression is a common experience for patients with advanced prostate cancer. Pain has previously been shown to significantly associate with overall survival in advanced prostate cancer. The McGill Pain Questionnaire (MPQ) (PPI score 0-2 versus 3-5) successfully stratified the survival of first line chemotherapy patients in TAX 327 (84,85).

The BPI-SF, a numeric rating scale (NRS), has been selected as the pain instrument for this study due to the high correlation of numeric rating scales with verbal descriptor scales (e.g. MPQ PPI) (86) and its prior use in other metastatic prostate cancer studies (87,88). The BPI-SF assesses both the intensity of pain and the interference in the patient's function caused by their pain (89). The BPI-SF data can potentially help illustrate the overall benefit of treatment on pain. Analgesic usage will be scored according to the WHO analgesic ladder: 0 for no analgesic, 1 for non-opioid analgesics (including NSAIDs, paracetamol / acetaminophen, antidepressants, and agents intended to treat neuropathic pain), 2 for opioids for moderate pain, and 3 for opioids for severe pain (90).

3. BACKGROUND THERAPEUTIC INFORMATION

Olaparib

Olaparib previously referred to as AZD2281 or KU-0059436 in earlier studies is a potent inhibitor of PARP-1. Olaparib shows significant monotherapy activity in tumour cells with defective components of HR, such as cells with the *BRCA1* *-/-* and *BRCA2* *-/-* genotype both preclinically and clinically (10,11,50,51,52,53,62,63). Selective tumour sensitivity to this PARP inhibitor has also been observed in tumour cells with loss of PTEN function and *ETS* gene rearrangements (41,42,44). This sensitivity in pre-clinical models is expected to translate to clinical benefit.

3.1 Pre-clinical Experience with Olaparib

This pre-clinical and clinical experience with olaparib (AZ2281, KU0059436) is fully described in the Investigator Brochure (IB). Key findings are summarised below.

Pharmacokinetic Data

The olaparib molecule shows cellular activity in the low nM range with a cellular dose for 50% inhibition (IC₅₀) of 2 nM in HeLa cells. Distribution of olaparib is typical for an orally administered foreign compound, in the gastro-intestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. The oral bioavailability of olaparib when dosed at 5mg/kg via a solution formulation was 17% and 19% in male and female rats and 79% *-/+* 12 in male dogs. An oral study of olaparib demonstrated bioavailability of >85% for both 5% and 20% w/w microionised dispersion of the drug substance in Gelucire. Following single oral dosing (5mg/kg), absorption was rapid with an AUC of 10.3 \pm 2.01 in

dogs. The estimated $t_{1/2}$ for olaparib was 3.0, 2.5 and 4.61 \pm 1.66 hours in female rats, male rats and dogs respectively. Multiple oral dosing of olaparib in 28-day rat and dog studies demonstrated that absorption was rapid and exposure increased greater than proportionally with dose across the dose range examined (upto 15mg/kg/ day in dogs and upto 40mg/kg in rats). Plasma protein binding of olaparib varied between 70.4% and 58.8% in rat and dog studies. Metabolism data to date is limited and further investigations are ongoing. To date, several metabolites have been observed in pre-clinical studies. Similar metabolite profiles were observed in the urine and faeces of male and female rats. Excretion is primarily via the faeces and to a lesser extent, the urine. In a study of [14 C]-olaparib in the rat, excretion was 76 \pm 13% in faeces and 20 \pm 11% in urine. For more detailed preclinical data please refer to the IB.

Toxicology and Safety Data

Olaparib has shown comparatively low toxicity in rodent and dog toxicology studies. Oral doses of olaparib were well tolerated for up to 6 months in safety studies and showed no cardiovascular, respiratory, central, peripheral and autonomic nervous system toxicity findings that were a concern. The toxicology studies indicate that the target organ of toxicity is the bone marrow. Specific *ex vivo* work has been conducted exposing human bone marrow cells to olaparib, which has confirmed that olaparib is also active against human bone marrow. The cytotoxic effect becomes evident at a higher concentration than that which fully ablates PARP activity (mean IC₅₀ of 2.7 μ M for myelosuppression [n = 4 human donors] compared with 0.1 μ M for total PARP-1 activity inhibition). These data, along with the 28-day dog and rat studies, show a myelotoxic effect that is mild-to-moderate and is reversible. Platelets appear first affected, followed by white blood cells. Importantly, oncology clinics are used to monitoring for the onset of such effects and are expert in their management.

Olaparib showed no mutagenic potential in the Ames test. Olaparib was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test, and was genotoxic in the rat micronucleus test. Reproductive toxicology data indicate that olaparib can have adverse effects on embryofetal survival and development at dose levels that do not induce maternal toxicity. These findings are not uncommon for many therapeutic agents used in oncology, and so do not present an unacceptable risk when appropriately clinically managed. For further details on these tests or on the fertility studies please refer to the IB.

3.2 Clinical Experience with Olaparib

3.2.1 Pharmacokinetic (PK), Pharmacodynamic (PD) Data

In the Phase I study, patients with solid tumours were given olaparib at a starting dose of 10mg for the first 14 days of a 21-day cycle with a subsequent protocol amendment, changing the dose schedule to continuous daily dosing starting at 100 mg BID for a 28-day cycle. Absorption was rapid and a peak plasma concentration was observed between 1-3 hours post dosing with a terminal elimination half-life of 6.10 hours, supporting twice daily dosing. Drug exposure increased dose proportionally with doses up to 100 mg but increase less than dose proportionally thereafter. The mean volume of distribution and mean plasma

clearance are approximately 40.3 L and 4.55 L/h. On multiple dosing, there was no evidence of any time dependency of the PK and no marked accumulation. Exposure increased proportionally with dose at doses up to 100 mg twice daily but increased in a less than proportional fashion at higher doses. There was no evidence of any marked ethnic difference in PK of olaparib between Japanese and Caucasian patients. Following dosing to cancer patients at doses of 400 mg BID, the population estimated maximum plasma concentration at steady state ($C_{max\ ss}$) ranged from 1.45 $\mu\text{g/mL}$ to 11.0 $\mu\text{g/mL}$ (3.34 μM to 25.3 μM , equivalent to unbound concentrations of 0.26 $\mu\text{g/mL}$ to 1.99 $\mu\text{g/mL}$ [0.6 μM to 4.58 μM]); the steady state area under the plasma concentration-time curve (AUC) (area under plasma concentration-time curve from zero to 12 h [AUC₀₋₁₂]) ranged from 6.56 $\mu\text{g}\cdot\text{h/mL}$ to 122 $\mu\text{g}\cdot\text{h/mL}$.

The distribution of olaparib is typical for an orally administered compound, in the gastrointestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Following administration of a radiolabelled dose of olaparib to cancer patients, olaparib accounted for approximately 70% of the circulating material in the plasma with the remainder accounted for by 3 other components (each accounting for approximately 10% of the material), all of which were also present in the excreta. Drug-related material was eliminated in the urine (35% to 50%) and in the faeces (12% to 60%) with 10% to 20% and 0.6% to 14% of the dosed material recovered in the urine and faeces as unchanged drug, respectively. A further 35 and 19 drug related components were excreted in the urine and faeces, respectively. The metabolites produced were predominantly a consequence of hydroxylation, oxidation or dehydrogenation of the piperazine carboxycyclopropyl, the flourophenyl and the phthalazinone ring system.

Evidence of inhibition of PARP-1 activity has been seen in peripheral blood mononuclear cells (PBMC) and tumour samples from patients dosed with olaparib at all dose levels studied (10 mg to 600 mg) but the data shows wide inter-individual variability in the extent of inhibition achieved and no evidence of any relationship between extent of inhibition and dose administered. Concentration-response curves for inhibition of PARP-1 activity in both PBMC and tumour samples have been generated from a population PK-PD analysis of the data. The population average maximal extent of inhibition in PBMC and tumour samples were 50.6% and 70%, respectively, with maximal inhibition achieved at plasma exposures (steady state AUC) in excess of 1 $\mu\text{g}\cdot\text{h/mL}$ (exposures which would be expected to be reliably achieved following doses of >40 mg). The potential clinical benefit of continuous dosing is supported by preclinical studies, which show that tumours re-grow after short-term use (e.g. 14 days) and that continuous PARP inhibition with olaparib was able to prevent tumour re-growth. The maximum tolerated dose of olaparib established in the Phase I trials was 400 mg twice daily, continuously (10).

3.2.2 Efficacy Data

The phase I study was enriched with *BRCA1* and *BRCA2* mutation carriers with advanced tumours in the escalation and expansion phase given the strong preclinical rationale of selective tumour killing in *BRCA1/2*-deficient cell lines. In the Phase I study, 41% of 46 evaluable patients with *BRCA*-mutant ovarian cancers achieved objective responses

(complete or partial responses) either by Gynecologic Cancer Intergroup (GCIIG) CA125 or RECIST criteria and a further 11% of patient's attained RECIST disease stabilisation (10,11). The encouraging clinical benefit rate of >50% in the subpopulation of *BRCA1/2* mutation cancer patients provides compelling evidence of single agent PARP inhibitor activity in *BRCA*-deficient cancer patients. Durable antitumour responses have also been reported in *BRCA* mutated breast and prostate cancer patients with one prostate patient ongoing treatment for more than 2 years (10, 11, 50, 51).

Two parallel open-labelled multicentre phase II studies of olaparib in *BRCA1/2* mutation carriers with advanced breast and ovarian cancer have confirmed the significant therapeutic efficacy of PARPi in this population (50, 51). 54 breast cancer patients and 56 ovarian cancer patients with advanced heavily pre-treated disease were recruited to 2 non-randomised sequential dose cohorts of 400mg and 100mg BID of olaparib. Following efficacy assessment of the 2 dose levels; patients on the 100mg BID cohort in both studies were allowed to increase the dose of olaparib to 400mg BID given the improved antitumour activity seen at the higher dose level. The breast cancer study reported an objective response rate (ORR) of 41 % (11/27) with 1 complete response (CR) and 10 partial response (PR)s and a median progression free survival (PFS) of 5.7 months (m) (range 4.6-7.4m) at 400mg BID in contrast to an ORR of 22% (6/27) with 6 PRs and a median PFS of 3.8m (range 1.9-5.5m) at the lower dose level (27). In the ovarian study, patients on the 400mg BID and 100mg BID dose levels showed an ORR of 33% (11/33) versus 13% (3/24) by RECIST criteria, a response by either RECIST or by GCIIG criteria of 61% (20/33) versus 17% (4/24) and a median duration of response of 290 days (range: 126-513 days) versus 269 days (range:169-288 days) respectively (50). Both dose levels demonstrated clinical activity, however the 400mg BID was more efficacious with improved outcomes establishing substantial antitumour activity for olaparib at a dose of 400mg BID in heavily pre-treated, *BRCA* mutant advanced breast and ovarian cancer patients (50,51). A further phase II study of olaparib at 400mg BID in patients with sporadic high grade ovarian cancer showed an objective response rate of 28%. This study provided the first clinical evidence for the antitumour activity of olaparib in sporadic serous ovarian cancers (62). Most recently, patients with sporadic platinum sensitive serous ovarian cancer who previously achieved either a partial or complete response from platinum therapy demonstrated a doubling of the progression free survival (PFS) from 4.8months to 8.4months with 400mg BID olaparib maintenance treatment compared to placebo. The hazard ratio (HR) was 0.35 (95% CI: 0.25, 0.49; p<0.00001) (63).

3.3 Summary of Clinical Toxicity Data

The clinical experience with olaparib is fully described in the IB and largely has been conducted with the Gelucire® 44/14 (capsule) formulation.

As of 20 May 2011, 1645 patients suffering from ovarian, breast and a variety of other advanced solid tumours had been exposed to olaparib across the dose range 10 mg daily to 600 mg BID, either as monotherapy (n=12 studies) or in combination with other chemotherapy agents (liposomal doxorubicin, cisplatin, dacarbazine, gemcitabine,

gemcitabine+cisplatin, carboplatin, carboplatin+paclitaxel, paclitaxel, topotecan, irinotecan, or bevacizumab).

Olaparib (in the capsule formation) appears to be generally well tolerated in patients with various solid tumours at doses up to and including 400mg bd, as monotherapy. Administration of Olaparib has been associated with reports of laboratory findings and/or clinical diagnoses of:

- Haematological toxicity:
 - Anaemia, generally mild to moderate (CTCAE grade 1 or 2)
 - Neutropenia, predominantly mild to moderate (CTCAE grade 1 or 2)
 - Lymphopenia, generally mild or moderate (CTCAE Grade 1 or 2)
 - Thrombocytopenia, generally mild or moderate (CTCAE grade 1 or 2), sometimes severe (CTCAE grade 3 or 4)
 - Mean corpuscular volume or elevation, generally mild to moderate (CTCAE grade 1 or 2)
- Nausea and vomiting, generally mild to moderate (CTCAE grade 1 or 2), intermittent and manageable on continued treatment
- Dyspepsia, generally mild or moderate intensity (CTCAE grade 1 or 2)
- Dysguesia, generally mild or moderate intensity (CTCAE grade 1 or 2)
- Fatigue, (including asthenia) generally mild or moderate intensity (CTCAE grade 1 or 2)
- Headache, generally mild to moderate intensity (CTCAE grade 1 or 2)
- Dizziness, generally mild to moderate intensity (CTCAE grade 1 or 2)
- Pneumonitis events with no consistent clinical pattern have been reported in a small number of patients with extensive previous exposure to chemotherapy
- Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML) have been reported very rarely in a small number of patients

From the completed studies, there are no safety concerns noted for the renal or hepatic parameters measured and no clinically significant changes of concern relating to coagulation parameters. The changes in haematological parameters (haemoglobin, neutrophils, and thrombocytes) are as expected for olaparib monotherapy or can be explained by co-existing conditions/previous chemotherapy.

Olaparib appears to be generally well tolerated at PARP inhibitory dose levels in the monotherapy clinical studies with predominantly mild toxicity. Thus it represents a potential advance in the treatment of advanced cancers by directly inhibiting PARP-1 and hence tumour growth as monotherapy.

Preliminary data from Phase I and Phase II studies of olaparib in combination with various chemotherapy agents indicate a substantial increase in neutropenia, thrombocytopenia and anaemia compared to giving these cytotoxic agents alone. These findings are consistent with pre-clinical findings. There are more severe haematological events i.e., CTCAE grade 4 neutropenia, febrile neutropenia and thrombocytopenia being reported as SAEs. When these toxicities occur it has been managed with routine clinical practise, including dose delays, dose reductions and intermittent doses and/or the use of supportive care measures such as G-CSF.

Final laboratory data from D0810C00002 (KU36-92) study have shown mean corpuscular volume (MCV) increases in approximately 30% of patients in the study, especially with prolonged treatment with olaparib (≥ 6 cycles of treatment). The MCV elevations were mild to moderate in intensity, observed in the 200 mg BID dose cohort and above and were asymptomatic in nature. There was no obvious correlation of MCV with haemoglobin, platelets or white blood cell (WBC) values for these patients, and there does not appear to be any clinical consequences. MCV has not been captured as a standard laboratory parameter within the olaparib Phase II studies D0810C00008 (KU36-44) and D0810C00009 (KU36-58), however elevations in MCV were also observed in a number of patients from these studies. The MCV elevations again appear to become progressively elevated over time. Elevations in serum amylase were observed in approximately 15% of patients from final laboratory study data from D0810C00002 (KU36-92). The majority of these increases (13%) were mild to moderate (CTCAE grade 1 or 2) with no apparent link to clinical symptoms. No new significant safety information has emerged from any other reported studies with respect to elevations in serum amylase.

Rare Adverse Events

Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML)

As of 27 August 2012 a total of 13 patients who received olaparib have had MDS and/or AML from 5 monotherapy studies (D0810C00002, D0810C00009, D0810C00012, D0810C00019 and D0810C00042) and 2 combination studies (D0810C00004 and D0810C00041) out of a total number of 1896 patients estimated to have received olaparib in the development programme to date (0.7%, 13/1896). Additionally, there have been 2 reports of MDS from 2 monotherapy studies (D0810C00012 [completed], D0810C00019 [ongoing: completed its primary analysis of PFS]) out of 304 patients that received placebo or comparator in the trial programme (0.66%): an AE of MDS was reported in a patient who received placebo in Study D0810C00019 (post PFS data cut-off); and MDS was reported as a secondary cause of death in a patient who received liposomal doxorubicin in Study D0810C00012.

The 13 olaparib-treated patients who reported MDS and/or AML received between 126 days and 1759 days of olaparib for ovarian/peritoneal cancer, prior to the diagnosis of MDS and/or AML. The MDS/AML events occurred post-discontinuation of olaparib treatment in 8 of the 13 patients and 8 patients died. All 13 patients had other potential contributory factors that

may offer an alternative explanation for the development of MDS/AML. Ten patients had a documented BRCA mutation that may predispose them to developing MDS and/or AML (Cole and Strair 2010). The ovarian/peritoneal cancers were diagnosed around 497 days to 4503 days prior to starting olaparib treatment. The majority of patients had been treated with extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents, (ranging from 6 to 95 cycles over periods of 6 months to 15 years). One patient had a family history of leukaemia.

Epidemiological studies from the literature have indicated a higher risk of therapy related MDS/AML in ovarian cancer populations, particularly those who received alkylating agents (Leone et al 1999, Travis et al 1999). Pedersen-Bjergaard et al (Pedersen-Bjergaard et al 1980) reported on the cumulative probability of developing AML over time, from 0 to 5 years of observation, in first line patients with ovarian carcinoma exposed to chemotherapy with alkylating agent Theosulfan. At 2 years the risk was 0.4% (± 0.4 standard error [SE]), at 3 years was 1.0% (± 0.7 SE) and 4 years 2% (± 1.2 SE). This illustrates the increasing risk of developing AML over time when exposed to chemotherapy. The cumulative incidence for developing MDS/AML post exposure to olaparib is currently 13 cases or 0.7% of the total exposed population, where average time from diagnosis of ovarian/peritoneal cancer to onset of the event is 5.9 years (range 2.6 to 12.7). The number of reports falls within those expected using the Pedersen-Bjergaard estimates of patients exposed to chemotherapy.

Pneumonitis

As of 27 August 2012, 1896 patients are estimated to have been exposed to olaparib. There have been 9 (0.5%) reported cases of pneumonitis or suspected pneumonitis.. Three were from monotherapy studies and 6 were from combination studies (3 with olaparib in combination with liposomal doxorubicin, and 1 each with olaparib + topotecan, olaparib + gemcitabine + cisplatin and olaparib + gemcitabine). These patients had a variety of cancer types including breast cancer, nonsmall cell lung cancer, small cell lung cancer and cancer of the thymus. All but one of these patients were hospitalised for the management of pneumonitis. Five of these patients have died; 2 from pulmonary insufficiency and 3 for disease progression. In summary, the 9 reported cases of pneumonitis presented with no consistent clinical pattern and were heavily confounded by a number of predisposing factors (including disease under investigation, underlying pulmonary disease, pre-existing medical conditions, smoking history and/or previous chemotherapy and radiotherapy). Additionally there have been 3 reports of pneumonitis out of 304 patients that received placebo or comparator in the trial programme (0.99%). The frequency of pneumonitis seen with olaparib treatment is consistent with the expected rates of pneumonitis in a cancer population (93-94).

Pre-clinical and Clinical Experience with New Melt-Extrusion (tablet) formulation

Melt-Extrusion (tablet) formulation has been developed to render the olaparib amorphous and presents the drug in a solid dispersion in copovidone (30% drug loading). The milled extrudate is then blended with pharmacopoeial excipients and compressed into a tablet.

The Melt-Extrusion (tablet) formulation, when dosed to fasted dogs at a 100 mg dose, shows at least 2.4 times the C_{max} & AUC than the Gelucire® 44/14 (capsule) formulation. In addition the Melt-Extrusion (tablet) formulation showed reduced pharmacokinetic

variability in the dog with CV of ~ 20% as compared to ~ 50% for the Gelucire® 44/14 (capsule) formulation. It is envisioned that the new Melt-Extrusion formulation of olaparib should provide a more bioavailable and patient friendly formulation by minimising the number of dosage units and providing a more consistent PK profile.

This olaparib Melt-Extrusion formulation (tablet) will be the formulation evaluated in the Phase III clinical programme and consequently this study will also be conducted with the olaparib tablet. There is an ongoing trial (D0810C00024) being conducted at the Royal Marsden NHS Foundation Trust and other centres to establish the comparative bioavailability of the tablet formulation compared with the capsule formulation. In addition single and multiple dose safety & tolerability data will be gathered.

Following single oral dosing with the tablet formulation, absorption was more rapid than the capsule. The C_{max} was typically achieved between 0.5 hours and 2 hours after dosing. Following the peak, plasma concentrations declined biphasically with the mean terminal $t_{1/2}$ of 6.97 hours. The mean volume of distribution of olaparib tablet was 54.9L and the mean plasma clearance was 542L/h. Both G_{mean} , C_{max} and AUC increased approximately proportionally with dose (8-fold and 12-fold, respectively, for a 10-fold increase in dose).

The relative bioavailability (BA) of the tablet formulation (compared to capsule) at the 3 lower dose levels studied are shown in Table 1. At the 2 lower tablet doses, although the C_{max} achieved after dosing with the tablet formulation tended to be higher than that with the capsule, when based on AUC, the BA of the 2 formulations was actually very similar. However, at the highest tablet dose (250 mg), the exposure delivered by the tablet formulation (both C_{max} and AUC) was higher than that delivered by the capsule.

Table 1: Relative bioavailability of tablet versus capsule formulation

Parameter	25mg tablet dose vs 50mg capsule dose	50mg tablet dose vs 100mg capsule dose	250mg tablet dose vs 400mg capsule dose
C_{max} ratio	1.29	1.53	2.49
95% CI	0.92-1.81	1.17-2.00	1.93-3.20
AUC ratio	1.03	0.99	1.74
95% CI	0.83-1.27	0.71-1.38	1.27-2.38

AUC, Area under the plasma concentration-time curve; CI, Confidence interval; C_{max} , Concentration maximum (plasma).

On multiple dosing, a 200mg tablet BID dose gave plasma exposure within the range of those achieved following 400mg BID capsule dose (6.88ug/ml vs 5.71 ug/ml) but the average AUC_{0-12} and C_{min} were lower (36.1ug/ml vs 43.1 ug/mL and 1.00ug/mL vs 1.86ug/mL, respectively) than achieved in a separate cohort of patients following the 400mg BID capsule dose. In addition, steady state data generated from a further cohort of patients randomised to BID dosing with both 200mg tablets and 400mg capsule dose (n=6) demonstrated that the 2 formulations could not be concluded to be bioequivalent (treatment ratio for C_{max} was 0.99 (90% CI:0.85 to 1.15) but for AUC_{0-12} was 0.79 (90% CI:0.65 to 0.94). Following multiple doses at 250, 300, 350 and 400mg BID, exposure continued to increase with dose. Please refer to the IB for further data on the tablet formulation.

The dose escalation phase of the ongoing Phase I bioavailability trial (D0810C00024) has been completed and has shown 400 mg BID to be the maximum tolerated tablet dose with frequent dose limiting toxicities being observed at higher doses. The study is now further evaluating the tolerability and clinical activity of two tablet doses - 300 mg BID and 400 mg BID. Preliminary data suggest that 400mg BID olaparib tablets is well tolerated over the first 4 weeks of treatment. In this trial the starting dose of olaparib tablets will be 400mg BID. It is envisioned that a proportion of patients will require dose reductions to 300mg BID, 200mg BID or 100mg BID respectively for cumulative toxicity over the course of several months of treatment.

4 TRIAL OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to evaluate the anti-tumour activity of olaparib in patients with advanced CRPC who have progressed following one or two chemotherapy regimens including taxane-based regimens.

4.2 Secondary Objectives

The secondary objectives are to evaluate:

- Radiological progression-free survival (rPFS)
- Time to radiological progression
- Progression free survival (PFS)
- Overall survival
- Time to PSA progression
- Duration of PSA response (decline of $\geq 50\%$)
- PSA objective response (PSA-ORR)
- The utility of CTCs as an early indication of benefit from PARP inhibitor therapy
- Further characterise the safety profile of olaparib in advanced CRPC patients

4.3 Tertiary/exploratory Objectives

- To evaluate clinical benefit as indicated by an improvement in pain measurements (BRI-SW)
- To evaluate DW-MRI imaging in selected patients and to correlate these results with PSA, CTC and radiological responses by conventional imaging

5 TRIAL ENDPOINTS

5.1 Primary Endpoints

Response rate:

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

- Objective response by modified RECIST (baseline lymph node size must be ≥ 2 cm to be considered a target lesion) (Appendix E) or
- Conversion of circulating tumour cell count (CTC) from $\geq 5/7.5$ ml blood at baseline to $< 5/7.5$ ml blood nadir confirmed by at least two readings 4 weeks apart or
- PSA decline of $\geq 50\%$ (according to the PCWG2) (Appendix D)

Failure will be defined as:

- Progression by RECIST – increase in measurable lesion size (S) or new lesion AND/OR
- Progression by bone scan (Appendix D)

5.2 Secondary Endpoints

- Radiological progression-free survival (rPFS)
- Time to radiological progression
- Progression free survival (PFS)
- Overall survival
- Time to PSA progression
- Duration of PSA response (decline of $\geq 50\%$)
- PSA objective response (PSA-ORR)
- Proportion of patients with conversion of CTC count to $< 5/7.5$ ml blood nadir
- Safety and tolerability profile of olaparib in patients with metastatic CRPC

5.3 Tertiary/exploratory Endpoints

- Impact of olaparib treatment on bone metastases imaged by DW-MRI in selected patients (optional) and to correlate these results with PSA, CTC and radiological responses by conventional imaging
- Proportion of patients achieving pain improvement

6 TRIAL DESIGN

This study is divided into 2 parts; Part A & B. Part A is an efficacy screening stage for sensitive biomarkers. It is designed as an open-labelled, non-randomised two stage design both to allow the activity of olaparib in unselected advanced CRPC patients to be evaluated and to permit the development of predictive biomarkers of response to olaparib. Part B is a subsequent validation stage which will be undertaken if confirmation of activity in a biomarker defined subgroup is necessary. It is an open-labelled, single stage assessment of anti-tumour activity of olaparib in preselected patients based on putative biomarkers of HR repair deficiency previously identified in Part A. A total of up to 89 evaluable patients will be enrolled to Parts A & B.

Patients with advanced CRPC who have consented to participate in this trial will be screened and enrolled into either Part A or Part B of the study depending on which part of the study is running at the time of patient enrolment. Patients will be administered oral olaparib tablets, 400mg BID continuously until disease progression is documented and confirmed (i.e., confirmed radiographic progression) or withdrawal for another reason (see section 10.10). Paraffin embedded tumour blocks or sections from the archival tumour tissue at the time of the original diagnosis or from a biopsy / resection of metastatic disease

is mandated from all subjects who enrol on the study. These samples should be obtained during the screening period after written informed consent has been obtained. All patients participating in this trial (Part A & B) will also have mandatory circulating tumour cells (CTCs), plasma and fresh tumour biopsies collected at pre-specified times during the study (Table 2). The tumour material will be analysed for biomarkers of sensitivity (response) to PARP inhibition. These tests will include *PTEN* and *ERG* expression, *ETS* gene rearrangements and *PTEN* deletions, markers of cell cycle, DNA damage and repair including geminin expression, RAD51 and gamma H2AX foci formation, etc. Other biomarkers identified to be relevant to HR pathway from other translational research may be studied in parallel. Response to treatment with olaparib will be correlated to all the biomarkers evaluated.

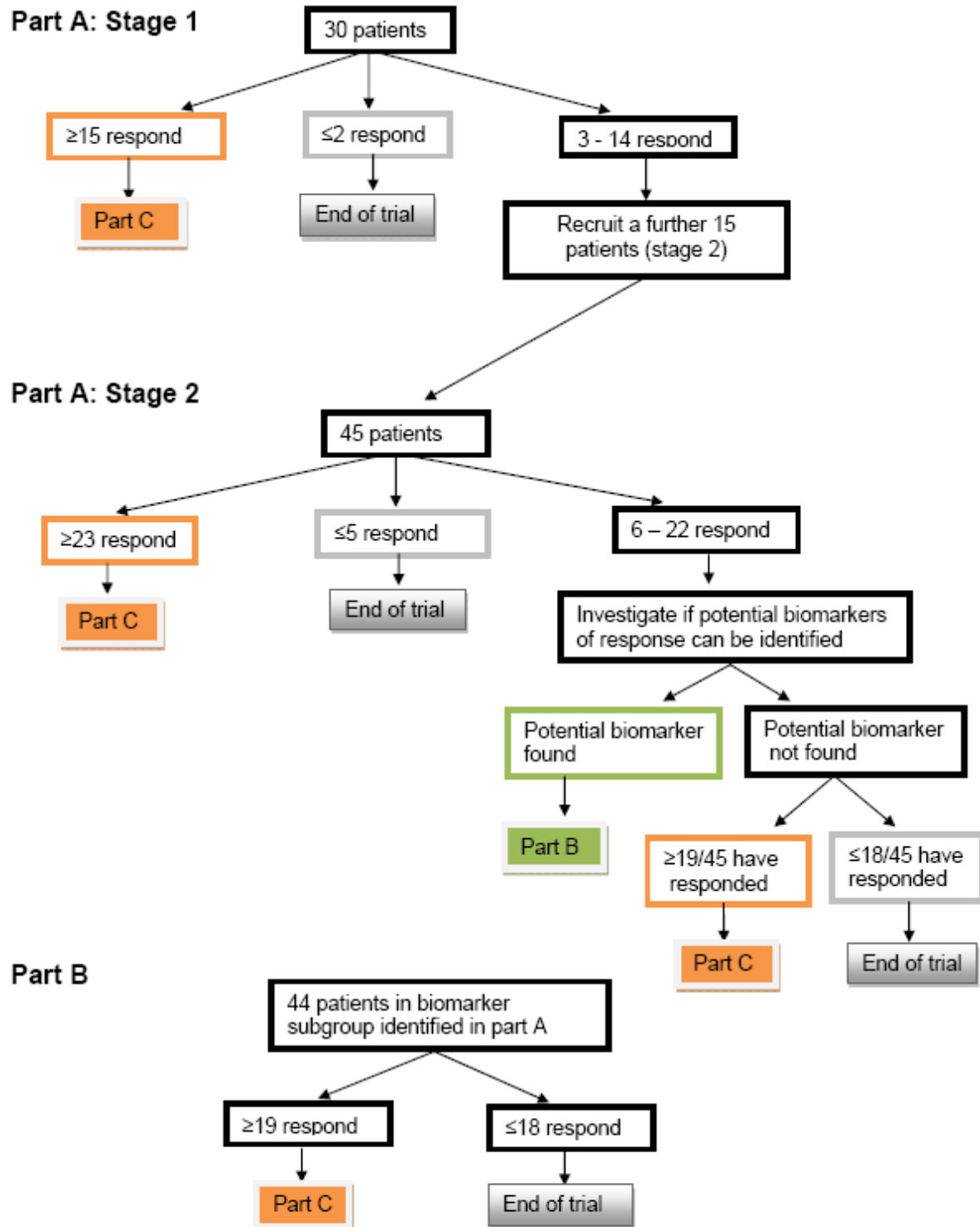
In PART A, accrual will be in unselected patients. The tumour tissue in responders versus non-responders from Part A will be evaluated to develop a molecular classifier for response to olaparib in CRPC patients that can then be utilised to select patients in Part B in the absence of evidence of a high overall response rate in PART A. Patients registered for Part B will be made aware that their tumour tissue will first be analysed for the relevant predefined biomarkers to determine their suitability for participation following consent in Part B of the study.

Disease status will be assessed at regular intervals during the course of the trial by CTC enumeration, computed tomography (CT) scan and / or on magnetic resonance imaging (MRI), diffusion-weighted MRI (DW-MRI), radionuclide bone scans and PSA. Each site should ideally designate the same reader who will evaluate the images for any one patient for the duration of the trial. Throughout the study, safety and tolerability will be assessed by the recording of adverse events; the monitoring of vital signs and physical examinations; and safety laboratory evaluations. Local laboratories will be used for the safety bloods. An independent Data Monitoring Committee (IDMC) will monitor safety data on an ongoing basis. Patient may continue on olaparib for as long as the patient is free of intolerable toxicity and is, in the opinion of the investigator, deriving clinical benefit. Patients may however elect to withdraw from the study at any point without prejudice to further treatment. Patients will have a safety follow-up visit 30 days +/-5 after their last dose of study drug for safety and end of treatment assessments.

Although outlined in the trial schema below, Part C is not currently included in this protocol but may be incorporated following completion of Parts A & B as an amendment to this protocol. PART C will be the subsequent randomised evaluation of olaparib versus an appropriate standard of care comparator to be decided at the time of initiating the amendment. Part C will only be initiated if there is sufficient evidence of antitumour activity observed either in the unselected or selected CRPC patients to warrant further evaluation of olaparib in a randomised setting. This will occur following the evaluation of safety, efficacy and biomarker analysis from Parts A and B by the Independent data Monitoring Committee (IDMC) and will involve a separate funding application and regulatory approvals. Patients in Part C may be either preselected patients based on the molecular determinants of response as identified in Parts A and B, or be unselected, depending on the response that has been seen in Parts A and B.

More details on the design of the trial can be found in the statistical considerations section.

6.1 Study Flow Chart



Part C will only be initiated if the anti-tumour activity observed in Parts A and B are sufficient to warrant a randomised study. The design of Part C will be determined following the analysis of Parts A/B.

Figure 3: Adaptive TOPARP Trial Schema

7 PATIENT SELECTION & ELIGIBILITY

Subjects with advanced progressing CRPC who have had either one or two previous lines of taxane-based chemotherapy will be invited to participate in the TOPARP study.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to safeguard the integrity of the study results.

7.1 Number of Patients

Part A: 30-45

Part B: 44

7.2 Source of Patients

Several oncology centres in the United Kingdom with extensive experience in conducting phase II/III trials have agreed to participate in this trial. Patients who have progressing castration-resistant metastatic prostate cancer will be offered participation in this trial.

7.3 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in the study:

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 archival tumour tissue available for molecular analyses. If the patient does not have a prior histological diagnosis then the planned baseline fresh biopsy may be used for both the purpose of confirming the histological diagnosis prior to trial entry and for subsequent biomarker analysis. All patients must be willing to have fresh biopsies to obtain tumour tissue for biomarker analysis
4. At least one but no more than two previous taxane-based 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:
 - At least 28 days since the completion of prior flutamide treatment. Patients whose PSA did not decline in response to antiandrogens given as a second line or later intervention will only require a 14 days washout prior to Cycle 1, Day 1.
 - 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.

- 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:
 - 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 $\geq 2 \mu\text{g/L}$ (2 ng/ml); patients on systemic glucocorticoids for control of symptoms must have documented PSA progression by PCWG22 while on systemic glucocorticoids prior to commencing Cycle1 Day1 of treatment.
 - 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 $< 50 \text{ ng/dL}$ ($< 2.0 \text{ nM}$). 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 $\geq 50\%$)
 9. Life expectancy > 12 weeks.
 10. Patient must be able to swallow a whole tablet.
 11. Patient and the patient's partner of childbearing potential, must agree to use medically accepted methods of contraception (e.g., 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 CTC count of ≥ 5 cells/7.5mls blood at screening confirmed by the central laboratory.
 14. Subjects must have adequate bone marrow, hepatic and renal function documented within 7 days of registration, defined as:
 - Haemoglobin $\geq 10\text{g/dL}$ independent of transfusions
 - White blood cells $> 3 \times 10^9/\text{L}$
 - Absolute neutrophil count $\geq 1.5 \times 10^9/\text{L}$
 - Platelets $\geq 100 \times 10^9/\text{L}$
 - Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) except for patients with known Gilbert's syndrome.
 - 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.
 - Serum creatinine $\leq 1.5 \times$ ULN or a calculated creatinine clearance $> 40\text{mL/min}$ for patients with creatinine levels above institutional normal. For GFR estimation, the Cockcroft and Gault equation should be used:
$$\text{GFR} = \text{CrCl (ml/min)} = (140 - \text{age}) \times \text{wt (kg)} / (\text{serum creatinine} \times 72)$$
 - Albumin $> 30 \text{ g/dl}$

7.4 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

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 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 have experienced a seizure or seizures within 6 months of study treatment or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in patients not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital (see Section 12.13)).
11. Patients receiving any of the following classes of inhibitors of CYP3A4 (see Section 12.13 for guidelines and wash out periods);
 - 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 investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's 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

7.5 Restrictions

1. Patients must refrain from fathering a child or donating sperm during the study and for 3 months following the last dose of olaparib. Patients of child bearing potential and their partners, who are sexually active must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after the last dose of study drug. Reliable methods of contraception should be used consistently and correctly. Acceptable methods of contraception to be used in this study include:
 - Condom with spermicide and one of the following:
 - Oral contraceptive or hormonal therapy (e.g. hormone implants)
 - Placement of an intra-uterine device
 - Acceptable non-hormonal birth control methods include:
 - Total sexual abstinence. Abstinence must be for the total duration of the study and for 3 months following the last dose of olaparib
 - Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
 - Tubal occlusion plus male condom with spermicide
 - Intrauterine Device (IUD) plus male condom and spermicide - Provided coils are copper-banded
 - Acceptable hormonal methods:
 - Etonogestrel implants (e.g., Implanon, Norplan) and male condom with spermicide
 - Normal and low dose combined oral pills+male condom with spermicide
 - Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
 - Intravaginal device and male condom with spermicide (e.g., EE and etonogestrel)
 - Cerazette (desogestrel) and male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.
2. No other chemotherapy or other novel agent is to be permitted during the course of the study with the exception of continued used of LHRH agonist. Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be adequately be managed with analgesics as long as the patient does not meet the criteria of disease progression or treatment discontinuation.
3. Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.
4. In vitro data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, **to ensure**

patient safety all patients must avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity (see Section 12.13) from the time they enter the screening period until 30 days after the last dose of study medication.

8 OVERVIEW OF STUDY PROCEDURES

8.1 Informed Consent

The study objectives, overall requirements, potential benefits and risk will be discussed with potentially eligible patients. Interested patients will be given a TOPARP patient information sheet. Consent must be obtained only after allowing the patient sufficient time for consideration, and the opportunity to ask any further questions. A signed, TOPARP written informed consent form must be obtained from the patient in accordance with local practice and regulations. Pre-entry tests, not performed routinely as part of standard patient management, will only be done after the TOPARP consent form has been signed and personally dated by both the patient and the Investigator. Confirmation of the patient's informed consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed form will be provided to the patient and the original retained in the investigator site file and must be available for verification by ICR-CTSU study staff or for regulatory audit/inspection at any time. Patients who consent on the TOPARP study, consent to having fresh tumour biopsies, archival tumour tissue, CTCs and plasma collected for molecular and biomarker studies.

Patients who wish to have diffusion weighted MRI (DW-MRI) scans to assess their disease during the study will be required to sign a specific DW-MRI consent form. Participation in this component of the study is entirely voluntary. Refusal to participate in the DW-MRI component of the study will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.

8.2 Registration

Once informed consent has been obtained, patients must be registered for screening by contacting the ICR CTSU:

To register a patient telephone ICR-CTSU
On: 0208 643 7150
(09.00 – 17.00 Monday to Friday)

The following information will be required when registering the patient:

- Name of cancer centre, treating hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent
- Patients initials and date of birth
- Confirmation of diagnosis

The patient will be allocated a unique registration number.

8.3 Eligibility status and trial entry

Once all screening evaluations have been completed, an eligibility checklist should be completed by the clinician/research nurse. The eligibility checklist should be completed for all patients registered.

For those patients who remain eligible, the clinician / research nurse should contact ICR-CTSU to confirm eligibility and obtain a trial number.

To confirm patient eligibility telephone ICR-CTSU

On: 0208 643 7150

(09.00 – 17.00 Monday to Friday)

The following information will be required:

- Patient's full name, hospital number, NHS number, postcode and trial registration number.
- Confirmation of the patient's eligibility status according to the eligibility checklist
- Confirmation that the evaluable disease being followed in the trial has been assessed by either CT or MRI and a bone scan within 28 days of scheduled start date of treatment
- Confirmation of consent for the trial

If the patient is confirmed as eligible for trial entry, the caller will be given the patient's unique trial identification number (Trial ID), and fax confirmation will be sent to the appropriate pharmacist to enable dispensing of the study drug.

A screening log should be completed for all registered patients who do not subsequently enter the study. This will record reasons for exclusion e.g. because screening tests identified that they were ineligible or the patient subsequently withdrew consent.

9 OVERALL STUDY ACTIVITIES

9.1 Screening Period

All patients must sign the TOPARP written informed consent before study specific screening procedures can be performed. Consent may be obtained up to 28 days prior to Cycle 1, Day 1. Patients will have a screening period of up to 28 days prior to Cycle 1 Day 1. The laboratory investigations (haematology, electrolytes, tumour markers, CTCs and testosterone level) must be performed within 14 days of starting treatment on olaparib. For details of the schedule and nature of the screening assessments, refer to Table 2 (page 56). All the screening assessments must be complete and eligibility criteria met prior to enrolment into the study. Patients who meet the eligibility and screening requirements will

return to the site for Cycle 1 Day1 visit. As part of the screening process, CTCs, a pre dose biopsy and blood samples will be collected for the predefined biomarkers of interest.

9.2 Treatment Period

All screening assessments must be completed and reviewed prior to the commencement of Cycle 1 Day 1 assessments. In the event that Screening and Cycle 1 Day 1 visits coincide, Cycle 1 Day 1 assessments do not need to be repeated. Olaparib at a dose of 400mg will be administered orally twice daily, once in the morning and once in the evening, continuously. Patients may receive continuous treatment for as long as they remain free from intolerable toxicity, and, in the investigator's opinion, are receiving clinical benefit. The patient will return on Day 8 and Day 15 of Cycle 1 and subsequently on the first day of each treatment cycle in order to evaluate safety, tolerability and dosing compliance. From Cycle 2 to end of study treatment patients' Day 1 visits will occur on a 28 day cycle with a +/- 2 day window. If the study window is utilised every effort will be made for the patient to return to schedule. Patients will have additional imaging visits up to 8 days before Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1, after every 3 cycles thereafter and treatment discontinuation. For details of the schedule and nature of the on-going assessments, refer to Table 2. The dose of olaparib may be reduced and/or a treatment delayed in patients experiencing toxicities according to the dose modification guidelines as set out in section 12.8. Safety parameters will be continuously followed-up during the duration of the trial.

9.3 End of Treatment (EOT) Visit

All patients will return for an end of treatment visit 30 +/-5 days from the time of last dose of treatment for safety and end of study treatment assessments. For details of the schedule and nature of the assessments for this end of study treatment visit, refer to Table 2 and section 11.2.5.

9.4 Follow Up Visits

Following treatment completion, patients will be followed for survival every 3 months.

10 OVERALL TRIAL ASSESSMENTS

10.1 Clinical Measurements

The Investigator will ensure that all data collected in the study are provided to ICR-CTSU. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the Electronic Case Report Form (eCRF) in accordance with instructions provided.

10.2 Medical History

Medical and Surgical History

Medical and surgical history, including a history of the disease being studied, other significant past and on-going conditions should be recorded. All previous radiotherapy and chemotherapy, as well as any other therapy received for prostate cancer, must be documented.

Recording of Concomitant Medications

The use of or any change in the patient's concomitant medications will be recorded when the patient visits the hospital (including a review of the patient's diary card for any self-administered medication).

Current Signs and Symptoms

Current signs and symptoms of the disease will be recorded, together with the appropriate NCI-CTC grade and causality, if appropriate.

10.3 Physical Examination

Evaluations should be performed by the same evaluator throughout the study whenever possible. A full physical examination will include the assessment of the body systems listed below and reporting if these findings were normal, abnormal or not done. A full examination will be conducted at the screening visit, cycle 1 day 1 and the end of study treatment visit. At all other times the extent of the examination beyond vital signs and weight will be conducted as clinically indicated. Height will be recorded at screening visit only. Vital signs include blood pressure, heart rate, respiratory rate, and oral or aural body temperature.

The following must be assessed and recorded:

- General appearance
- Cardiovascular
- Respiratory
- Gastrointestinal
- Genitourinary
- Central Nervous System
- Dermatological
- Musculoskeletal
- Peripheral lymph nodes
- Other

10.4 ECG Monitoring

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the Investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. An ECG assessment will be performed at screening as a baseline assessment. Subsequent ECGs will only be performed if clinically indicated.

10.5 Brief Pain Scores

The BPI-SF will be self-administered in the clinic to the patients on the first day of each treatment cycle and the results recorded in the patient's notes (Appendix I)

10.6 Blood, Tissue and Other Sampling

Blood samples for safety assessments will be done at the local institutes. Tests relating to biomarker work on CTC, plasma and tumour material will be performed primarily at The Institute of Cancer Research Cancer Biomarkers Laboratory. Samples will be collected and processed according to specified detail in the TOPARP Laboratory Manual. There may be a requirement to send some of the samples to be processed in a different laboratory. This will be done with contractual agreements in place and patient details will remain confidential.

Bone marrow or blood cytogenetic analysis may be performed according to standard haematological practice for patients with prolonged haematological toxicities as defined in Section 3.3. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to ICR-CTSU (see section 13).

Routine clinical laboratory tests will include the following;

Table 1: List of Laboratory Tests

Local Laboratory Tests		
<p>Haematology:</p> <ul style="list-style-type: none"> • Neutrophils • Haemoglobin (Hgb) • Platelet count with differential • White blood cell (WBC) count • Lymphocytes • Coagulation Factors: Prothrombin Time (PT), Partial Thromboplastin Time (PPT), International Normalized Ratio (INR) 	<p>Serum Chemistry:</p> <ul style="list-style-type: none"> • Albumin (ALB) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT;SGPT) • Gamma-glutamyltransferase (GGT) • Amylase • Aspartate aminotransferase (AST;SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Chloride (Cl) • Creatinine (Cr) • Glucose • Lactate dehydrogenase (LDH) • Magnesium • Phosphate • Potassium (K) • Sodium (Na) • Total bilirubin • Total protein • Uric acid • Bicarbonate 	<p>Urinalysis dipstick for:</p> <ul style="list-style-type: none"> • Blood • Protein • Glucose • (Microscopic examination if abnormal) <p>Additional laboratory tests:</p> <ul style="list-style-type: none"> • Prostate specific antigen (PSA) • Serum testosterone • Neuron specific enolase • Chromogranins <p>In the event of protracted myelosuppression:</p> <ul style="list-style-type: none"> • Bone marrow or blood cytogenetic analysis
Central Laboratory Tests		
<ul style="list-style-type: none"> • Circulating Tumour Cells (CTCs) for enumeration & molecular characterisation • Circulating tumour DNA 	<ul style="list-style-type: none"> • Circulating tumour microRNA (miRNA) • Plasma for biomarkers 	<ul style="list-style-type: none"> • Mandatory tumour biopsy • Urine telopeptides

10.7 Efficacy Measurements

CT or MRI Scan Assessments (Modified RECIST)

Baseline contrast-enhanced CT of the chest, abdomen and pelvis should be performed for the assessment of measurable lesions. Where contrast is contraindicated then either an MRI of the chest, abdomen and pelvis or a non-contrast CT scan can be performed if the

measurable disease is easily discernable without contrast. All baseline CT will be performed during the 28-day screening window as close as possible to Cycle 1, Day 1 of treatment. The CT scans will be repeated up to 8 days before Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3rd cycle subsequently (Table 2). CT scans may be performed earlier if clinically indicated. Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed for the purposes of the study if they were performed within the correct time frame and are of sufficient quality. Subsequent, repeat imaging requires the same method of assessment to characterise each identified lesion at baseline and during follow-up. Response categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) (refer to Appendix E) will be assigned at the scheduled visits. In the case of stable disease, measurements must have met the stable disease criteria at least once after study start for a minimum interval of 12 weeks. PR or CR by RECIST must be confirmed with a repeat tumour assessment 4 weeks after the criteria for response was met.

For the purposes of analysis, overall response using Investigator measurements of target lesions, assessment of non-target lesions and new lesions collected on the eCRF to derive the best overall response, and other protocol endpoints using these data. All medical images and tumour response assessments will be collected and retained on site as source data. A central image review may be performed by the sponsor if required.

Bone Scan Assessments

Bone scans will be used to assess bone lesions. Baseline bone scans will be performed during the 28 day screening window as close as possible to Cycle 1 Day 1, and up to 8 days prior to Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3rd cycle subsequently (Table 2). Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed as the baseline study if they were performed within the correct time frame and are of sufficient quality. **Bone deposits will be reported as absence or presence of new bone lesions. New lesions at the first scheduled reassessment at Week 12 must be confirmed by a second scan performed 6 or more weeks later. Disease progression by bone scan will be defined as two new bone lesions at the first 'progression' scan, confirmed by a further scan at least 6 weeks later (see section 10.9 for more details).** All medical images and tumour response assessments will be collected and archived locally. A central image review may be performed.

Diffusion weighed-MRI (DW-MRI) Scan Assessments

DW-MRI constitutes an optional component of the study. DW-MRI provides additional information regarding tumour cellularity and tumour cell death that cannot be evaluated with other imaging techniques. DW-MRI will be obtained at baseline (screening), up to 8 days prior to Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3 cycles subsequently. These results of these scans will not be utilized for the purpose of assigning disease status. Patients who wish to participate in this optional component of the study will be required to sign a separate Patient Informed Consent Form (PICF).

PSA Measurements

PSA will be assessed at baseline and routinely on day 1 of every 3rd cycle (12 weeks) by PCWG2 criteria (refer to Appendix D). Increases and decreases will be tracked in order to assess PSA responses. PSA changes from baseline to 12 weeks (either increment or decline) and maximal change in PSA will be recorded. Responses by PCWG2 criteria must be confirmed 28 days later.

Although serial PSA will be measured on this study and PSA progression documented by the PCWG2 criteria, the PSA value on its own is not considered a reliable measure of clinical benefit and does not correlate tightly with survival. PSA flares may occur early in the treatment and may therefore confound response assessment. Additionally, there is emerging data that PARP-1 is implicated in multiple other essential cellular functions separate from DNA repair including *ETS* gene-mediated transcription regulation which may have a bearing on the response assessments by PSA. PSA reading should not be applied as the sole criteria to consider treatment discontinuation. In absence of evidence of radiological or clinical evidence of disease progression, patients should continue in the study despite an increment in PSA. **Overall, therefore patients will not be taken off trial purely for rising PSA levels in the absence of worsening scans and symptoms since PARP inhibitors are likely to impact tumour growth without impacting PSA secretion.**

PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG2 criteria:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA from screening (baseline) PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- For patients with PSA declines at Week 13, the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. For patients with no PSA declines at Week 13, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented, which is confirmed by a second consecutive value four or more weeks later.

CTC Conversion Rate

CTCs will be obtained at various time points before, during and after treatment for enumeration and molecular characterisation (Table 7). CTC enumeration will be performed at The Institute of Cancer Research laboratories using the analytically valid CellSearch system (Veridex, LLC). For patients with baseline CTC counts of ≥ 5 cells/7.5 ml of blood, a conversion is defined as a nadir decline in the CTC count to < 5 cells/7.5 ml of blood. The conversion of CTC counts that are ≥ 5 to < 5 and percentage decline of $\geq 30\%$ indicative of clinical benefit and improved survival outcome will be measured (76,77,78).

A central review of bone scans and CT scans will take place. Anonymised copies of bone and CT scans should be sent to ICR-CTSU for central review on their request.

10.8 Safety Measurements

Safety parameters will be continuously assessed throughout the study prior to each cycle of treatment. These will include:

- Medical history, vital sign measurements, physical examination, and body weight
- Haematology, clinical chemistry, urinalysis
- Eastern Cooperative Oncology Group (ECOG) performance status
- Assessment of concomitant medications
- Adverse events (AEs) and serious adverse events (SAEs) including laboratory test AEs will be graded and summarised according to the NCI CTCAE version 4.02

10.9 Criteria For Discontinuation Of Study Treatment

The consensus guidelines of the PCWG2 recommend that confirmed radiographic progression is the most reliable indicator of clinical benefit in patients with CRPC. Based on this consideration, patients should be maintained on study treatment until confirmed radiographic progression or clinical progression or if the treating physician decides to initiate new systemic anti-cancer therapy. It is recommended that if the patient has PSA progression but no unequivocal clinical or radiological progression and an alternate treatment is not indicated, the investigators should maintain the patient's treatment until radiological disease progression is documented and confirmed. However, if the patient has unequivocal clinical progression without radiographic progression, these patients could be considered for other therapy at the discretion of the treating physician. In this circumstance, study treatment should be stopped and the patient advised regarding available treatment options. The intent of these criteria is to maintain study treatment for patients with PSA progression, given the absence of alternative treatment options available to participants who have failed both castration and chemotherapy and the high likelihood that some clones of prostate cancer may be benefiting in the context of radiological stability despite a PSA rise.

A patient is considered to have progressed on study if one or more of the following findings occur:

1. Progression by bone scan:

- The first bone scan with ≥ 2 new lesions compared with baseline is observed ≤ 13 weeks from cycle 1 day 1 and is confirmed by a second bone scan taken ≥ 6 weeks later showing 2 additional new lesions (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan)
- The first bone scan with ≥ 2 new lesions compared with baseline is observed > 13 weeks from cycle 1 day 1 and the new lesions are verified on the next bone scan ≥ 6 weeks later (i.e. a total of ≥ 2 new lesions compared with baseline).

2. Progression of soft tissue /visceral disease by modified RECIST:

- A patient will be determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions by modified RECIST. **Lymph nodes have to be >2 cm in size to be deemed measurable.**

3. Unequivocal evidence of clinical progression:

A patient can be taken off study at the discretion of the treating physician under the following circumstances:

- Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumour progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to grade 3 or higher felt by the investigator to indicate clinical progression
- Felt to be in the best interest of the patient to come off study due to clinical progression

4. Death from any cause.

When study treatment is discontinued due to unequivocal clinical progression, attempts should be made to determine the patient's status at the End of Treatment Visit to assess for radiographic progression, including a confirmatory bone scan, as deemed appropriate by the treating team.

10.10 Withdrawal from Study Treatment

Criteria for withdrawal of study treatment are outlined below:

1. Patient Withdraws Consent

Patients have the right to withdraw from the study at any time, without prejudice to their medical care, and are not obliged to state their reasons. If the patient withdraws consent, he should be encouraged to have a complete End of Treatment (EOT) visit and effort should be extended to clarifying the reason for the withdrawal.

Investigator may choose to withdraw a patient at any point if this is considered to be in the patient's best interest. The patient must be discontinued from the study treatment due to any of the safety reasons outlined below:

2. Sustained or Recurrent Unacceptable Side Effects:

- Any grade 3 or 4 events that have not reverted to grade 1 or the baseline (Cycle 1 Day 1) grade after a 42 days break off treatment with appropriate medical intervention. At the Investigator's discretion, patients may be considered for dose reductions [see Section 12.8 for management of toxicity & dose adjustments, providing they have not already undergone 2 dose reductions to 300 mg BID and 200 mg BID. If the grade 3 or 4 adverse events recurs at the lowest dose level (100 mg BID) then the patient must be discontinued].
- Unacceptable adverse events or any other toxicity in the investigator's opinion.
- Serious intercurrent illness or significant worsening of intercurrent illness that prevents further administration of treatment.
- A severe drug reaction or a hypersensitivity reaction to olaparib.

3. Non-compliance with Dosing or Trial Protocol Requirements

Patient is unable to adhere to study visit schedule or comply with protocol requirements despite several reminders about the requirements and efforts made to identify and resolve the aetiology of the problem may be discontinued at the discretion of the Investigator.

4. Progressive Disease

Evidence of clinically significant progressive disease as defined in section 10.9.

5. Use of Prohibited Concurrent Medication

The patient will be discontinued from the protocol treatment when prohibited drug is administered. Supportive care medications are permitted with their use following institutional guidelines.

6. Other Reasons

Additionally, patients may be discontinued from study treatment for any of the following reasons:

- Patient lost to follow-up
- If in the opinion of the Investigator, a change of therapy would be in the best interest of the patient
- Major protocol violation
- Incorrectly enrolled patients, i.e., the patient does not meet the required inclusion/exclusion criteria for the study

Attempts should be made to contact any patient failing to return for a scheduled visit/follow up, in order to ensure that the reason for not returning is not an adverse event. Likewise attempts should be made to establish whether any patient declaring a desire to discontinue

from the study e.g. for personal reasons, is in reality due to an adverse event (AE). If the olaparib therapy is prematurely discontinued, the primary reason for discontinuation must be recorded in the appropriate section of the eCRF. Patients will be required to attend an end of treatment visit at least 30 +/- 5 days after discontinuing study medication for collection and/or completion of AE information. All new events occurring during this 30-day period must be recorded (if SAEs they must be reported to the ICR-CTSU within 24 hours) and followed-up to resolution, unless in the opinion of the Investigator, the condition is unlikely to resolve due to the patients' underlying disease. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the Investigator assesses as possibly related to the study medication should also be reported as an AE. The patient should return all study medication following cessation of the study drug.

In the unlikely event that a patient withdraws consent for further follow-up data to be collected, the appropriate form in the eCRF should be completed and returned to ICR-CTSU. Clarification should be sought to ensure that the patient is not simply withdrawing from study drug. In the extremely unlikely event that the patient wishes to have their data removed from the trial completely (the implications of this should be discussed with the patient to ensure that this is their intent), this should be indicated as such on the form.

10.11 Patient Replacement Policy

An evaluable patient is defined as a patient who:

- Meets all of the inclusion and exclusion criteria specified in Sections 7.3 and 7.4 within the specified time frame;
- Has adequate histological tissue for the biomarker analysis.
- Completes twelve weeks of treatment with olaparib or experiences an event defined as treatment failure within twelve weeks.

Patients who prematurely withdraw from the study for reasons other than treatment failure may be replaced. Patients who become non-evaluable e.g. by ceasing to take LHRH agonists, may also be replaced. Replacement of ineligible and non-evaluable patients will be dependent on authorisation by the Independent Data Monitoring Committee (IDMC)

Note: Rising PSA or worsening bone scans in the first 12 weeks is NOT treatment failure and may reflect a flare response.

11 TRIAL ASSESSMENTS BY VISIT

Access to the electronic case report form (eCRF) will be provided by ICR-CTSU for each patient eligible for the trial. The relevant eforms should be completed at each hospital visit.

Note: some of the scheduled blood samples collected at screening, C1D1, C1D8, C2D1, C3D1, C6D1 and end of treatment require the patient to be fasted for 8 hours prior to sampling (see section 14.3 for further details).

11.1 Baseline Assessments

11.1.1 Screening

Screening activities that involve imaging and collection of archival and fresh tumour tissue will be conducted within a 28-day window prior to commencing Cycle 1 Day 1. All other screening activities/procedures outlined below will be conducted during the screening period over 14-days prior to Cycle 1 Day 1.

- Obtain archival tissue for analysis of biomarkers (Days -28 to Day 1) Please refer to section 15, for further details of specimens to be collected.
- Obtain mandatory fresh tumour biopsy (Days -28 to Day 1). Please refer to section 15, for further details of specimens to be collected.
- Medical history including details of the following:
 - All co-morbidities
 - Oncology history / family history of cancers
 - Prior prostate cancer history including extent of disease (stage), Gleason score at diagnosis, PSA levels
 - Previous hormonal, cytotoxic, and experimental treatments with start and stop dates
- Demographics
- Listing of current baseline signs and symptoms with associated NCI Common Terminology Criteria for Adverse Events grading (0-4)
- Physical examination
- Weight, and height
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG Performance Status
- 12 lead ECG
- Local Laboratory tests:
 - FBC: WBC with differential count, RBC, haemoglobin, hematocrit, platelets.
 - Coagulation studies (PT/PPT, INR)
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, uric acid, and magnesium

- Urinalysis: routine dipstick. Only if the dipstick is abnormal will the urine be sent for analysis
- PSA: If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE
- Serum testosterone
- Baseline tumour assessment
 - CT and / or other imaging procedures as clinically indicated
 - Bone Scan
 - DW-MRI (optional)
- Pain (BFI-SF) and Analgesic Usage Score
- Concomitant medications listing
 - Obtain a complete list of all prescription and nonprescription (over the counter) medications currently taken including pain medications. This also includes any nutritional supplements and/or herbal preparations.
- Assessments of signs and symptoms
- Research Biomarkers
 - Circulating Tumour Cell (CTC) blood collection for enumeration and molecular characterisation
 - Circulating Plasma DNA and RNA studies
 - PAXgene mirRNA studies
 - Urine markers of bone turnover and RNA
 - Serum Proteomic studies
 - Plasma and urine metabolomics studies
 - Buccal swab for DNA studies
 - Saliva for DNA studies

11.1.2 Cycle 1 Day 1

Patients who are eligible after screening and who accept to be entered into the study should be entered within 28 days of informed consent. All the screening assessments should have been completed and screenings results reviewed prior to trial entry and the commencement of Cycle 1.

The following procedures should be carried out **prior to dosing of study treatment**:

- Update listing of current baseline signs and symptoms with associated NCI Common Terminology Criteria for Adverse Events grading (0-4)
- Updated oncology history with any events that may have transpired since screening
- Physical examination
 - Full examination
 - Vital signs including blood pressure, heart rate, respiratory rate, oral body temperature
 - Height and weight
- Assessment of ECOG Performance Status

- Local Laboratory Tests:
 - FBC: WBC, RBC, haemoglobin, haematocrit, platelets with differential count.
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, uric acid.
 - Urinalysis: routine dipstick. Only if the dipstick is abnormal will the urine be sent for analysis.
 - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
- Pain (BFI-SF) and Analgesic Usage Score
- Concomitant medications listing
 - Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations
- Assessment of adverse events
- Research Biomarkers
 - Circulating Tumour Cell (CTC)
 - Circulating plasma DNA and RNA studies
 - PAXgene miRNA studies
 - Urine markers of bone turnover (telopeptides) and RNA
 - Serum proteomic studies
 - Plasma and urine metabolomics studies

11.2 On-treatment Assessments

11.2.1 Cycle 1 Day 8 Visit

The following assessments should be carried out on Day 8:

- Brief history and physical examination as clinically indicated
- Vital signs including blood pressure, heart rate, respiratory rate, oral body temperature
- Assessment of ECOG Performance Status
- Local Laboratory Tests:
 - Full blood count including WBC, haemoglobin, platelets
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, uric acid, magnesium
- Concomitant Medications listing:
 - Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations
- Adverse events will be monitored throughout the study. At each post-baseline visit, the investigator will begin by querying for adverse events by asking each patient a general,

non-directed question such as ‘How have you been feeling since the last visit?’ Directed questioning and examination will then be done as appropriate.

- Dosing compliance check
- Obtain post treatment mandatory fresh tumour tissue biopsy (Cycle 1 Days 8 to Day 28)
- Research Biomarkers
 - Circulating Tumour Cells (CTC)
 - Circulating plasma DNA and RNA studies
 - Plasma and urine for metabolomics studies

11.2.2 Cycle 1 Day 15 Visit

- Research Biomarkers
 - Circulating Tumour Cells (CTC)

11.2.3 Day 1 of Cycles 2, 3, 5, 6, 8, 9, 11, and 12 (Continue every cycle beyond Cycle 12)

The following assessments should be carried out at the indicated time point:

- Brief history and physical examination as clinically
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Weight
- Assessment of ECOG Performance Status
- Concomitant Medications listing
 - Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations.
- AE evaluation and recording at each post-baseline visit
- PSA measurements will be conducted every 12 weeks. PSA results will be assessed according to PCWG2 criteria
- Dosing compliance check and a count of study medication will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not 100% in the absence of toxicity, patient should be re-instructed regarding proper dosing procedures
- Pain (BFI-SF) and Analgesic Usage Score (each cycle)
- Local Laboratory Tests:
 - FBC: WBC, RBC, haemoglobin, haematocrit, platelets with differential count
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, LDH, uric acid, magnesium

- Research Biomarkers
 - CTC collection (Cycles 2, 3, 4, 7, every 3rd cycle thereafter and at treatment discontinuation/EOT)
 - Plasma for DNA, RNA studies (Cycles 2, 3, 5 and at treatment discontinuation/ EOT)
 - Paxgene miRNA studies (cycle 3, 5 and at treatment discontinuation/ EOT)
 - Urine and plasma metabolomics (cycles 2, 3 ,6 and at treatment discontinuation/EOT)
 - Urine markers of bone turnover and RNA (cycle 3, cycle 6 and at treatment discontinuation/ EOT)

11.2.4 Cycles 4, 7, and 10 and Treatment Discontinuation (continue every 3rd cycle beyond Cycle 10)

In preparation for the study visit, the following assessments should be conducted up to 8 days prior to the indicated visit. Results should be available for review at the Cycle 4, 7, or 10 Day-1 visit and every 3rd cycle beyond Cycle 10.

- CT Scan
- Bone Scan
- DW-MRI (optional)
- Other imaging procedures should be conducted as clinically indicated

At the study visit the following assessments should be conducted:

- Brief history and physical examination as clinically indicated
- Vital signs including blood pressure, heart rate, respiratory rate and oral body temperature.
- Weight
- Assessment of ECOG Performance Status
- Local Laboratory Tests
 - FBC: WBC, RBC, haemoglobin, platelets with differential count, chemistry with electrolytes: sodium, potassium, chloride, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, glucose, LDH, uric acid, magnesium, random glucose.
 - PSA (every 12 weeks): If patient undergoes a DRE, then PSA must be sampled prior to the DRE
- Concomitant medications listing
- AE evaluation and recording
- Dosing compliance check
- Pain (BFI-SF) and Analgesic Usage Score (each cycle)

- Review of imaging results (CT and bone scan) should be conducted and disease response /progression ascribed at the actual study visit (Cycle 4, 7, or 10 Day 1) unless otherwise indicated.
- Tumour biopsy (this end of study treatment biopsy is optional and can be collected at any point from treatment discontinuation up to the end of treatment visit).
- Research Biomarkers
 - CTC collection (Cycles 2, 3, 4, 7, every 3rd cycle thereafter and at treatment discontinuation/EOT)
 - Plasma for DNA, RNA studies (Cycles 2, 3, 5 and at treatment discontinuation/EOT)
 - Paxgene mirRNA studies (cycle 3, 5 and at treatment discontinuation/EOT)
 - Urine and plasma metabolomics (cycles 2, 3, 6 and at treatment discontinuation/EOT)
 - Urine markers of bone turnover and RNA (cycles 3, 6 and at treatment discontinuation/EOT)
 - Serum proteomic studies (at treatment discontinuation/EOT)

11.2.5 End of Treatment (EOT) Visit

Patients should return for an EOT visit 30 days +/- 5 following the patient's last dose of drug. The following assessments should be carried out at the EOT visit:

- Physical examination and weight
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature.
- Assessment of ECOG Performance Status
- 12-lead ECG is not mandated but should be done if clinically indicated
- Local Laboratory tests:
 - FBC: WBC, haemoglobin, platelets with differential count
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, LDH, uric acid, magnesium.
 - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
 - Disease Progression Assessment Review of imaging (CT, Bone scan, DW-MRI) results assessment according to modified RECIST and PCWG22 criteria.
 - Review of PSA results conducted over the course of the study and PSA progression assessment according to PCWG2 criteria
- Concomitant medications listing: update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations.
- Adverse events
 - AE follow-up to determine if any new or ongoing drug-related AE or any SAE regardless of relationship to study drug exists is required for 30 days post last

dose or until patient receives anticancer therapy, whichever comes first

- Final dosing compliance check if not performed when treatment discontinued.
- Pain (BFI-SF) and Analgesic Usage Score
- Research Biomarkers
 - Circulating CTC collection (if not obtained at treatment discontinuation)
 - Circulating plasma for DNA, RNA studies (if not obtained at treatment discontinuation)
 - Paxgene mirRNA studies (if not obtained at treatment discontinuation)
 - Urine and plasma metabolomics (if not obtained at treatment discontinuation)
 - Urine markers of bone turnover and RNA (if not obtained at treatment discontinuation)
 - Serum proteomic studies (if not obtained at treatment discontinuation)

11.2.6 3 monthly follow up (3 monthly from EOT)

Following treatment completion, patients will be followed for survival. Additional information as to whether they have started any platinum-based chemotherapy, mitoxantrone or another PARP inhibitor will be obtained where feasible. Follow-up data may be collected by a telephone interview.

11.3 Unscheduled Visits

Unscheduled visits and procedures may be conducted at the investigator's discretion for the safety follow-up of the patient. Such visits and procedures must be fully recorded in source documents regarding the purpose and outcome of the visit/assessment. Clinically significant laboratory results from unscheduled visits should be documented in the eCRF.

11.4 Early Discontinuation

Patients will be advised in the written informed consent form that they have the right to withdraw from study drug treatment at any time without prejudice, or may be withdrawn at any time at the discretion of the investigator or the sponsor. Notification of early patient discontinuation from the study and the reason for discontinuation will be made on the protocol deviation form provided. Patients removed from therapy for any reason should continue to be followed for the collection of safety data as outlined in the EOT visit procedures. For patients who refuse or are unable to attend further clinic study visits, telephone contact should be attempted to follow up for adverse events 30 days +/- 5 days after the last dose of study drug. All serious adverse events will be followed until resolution, until the event has stabilised and/or become chronic, until it has been determined that the event was caused by aetiology other than the study drug, or through 30 days, whichever comes first. Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete study-related assessments and retrieve any outstanding data and study drug. Such efforts should be documented in the source documents.

Table 2: Schedule of Procedures and Clinic Visits

Procedures & Assessments	Screening		Cycle 1	Cycle 1	Cycle 1	Cycle 2, 3, 5, 6, 8, 9, 11, 12	Cycle 4, 7, 10, every 3 rd cycle	Cycle 4, 7, 10, and every 3 rd cycle	End of Treatment (EOT) Visit	Follow Up
	Day -28 to Day -1	Day -14 to Day -1	Day 1	Day 8	Day 15	Day 1	Up to 8 days before	Day 1	Day 30 after last dose of drug	3 monthly from EOT
Informed Consent ¹	X									
Medical History ²		X								
Obtain Archival Tissue ³	X									
Tumour Biopsy ⁴	X			X(8± 21 days)					X (optional)	
Assessment of Symptoms ⁵		X	X	X		X		X	X	
Dosing compliance ⁵				X		X(every cycle)		X		
Concomitant medication ⁵		X	X	X		X		X	X	
Adverse events ⁵			X	X		X		X	X	
Physical Examination & Vitals ⁶		X	X		X	X		X	X	
Complete Pain Questionnaire ⁷		X	X			X(every cycle)		X(every cycle)	X	
12 Lead ECG ⁸		X								
Safety Bloods ⁹		X	X	X		X		X	X	
Testosterone Level ¹⁰		X								
PSA Levels ¹¹		X	X					X	X	
Neuron specific enolase/chromogranins ¹²		X								
Imaging Assessments										
Bone Scan ¹³	X						X			
DW-MRI (optional) ¹⁴	X						X			
CT Scan ¹⁵	X						X			
Disease Progression Assessment ¹⁶	X							X	X	
Survival & further treatment										X
Biomarker Tests (patients should be fasted for at least 8 hours prior to blood draw – see 14.3)										
Buccal Swab ¹⁷		X								
Saliva ¹⁸		X								
Plasma DNA & RNA ¹⁹		X	X	X		X (C2,3,5)			X	
Circulating Tumour Cells ²⁰		X	X	X	X	X (C2, 3)		X	X	
Blood miRNA ²¹		X	X			X (C3,5)			X	
Plasma Proteomics ²²		X	X						X	
Plasma and urine Metabolomics ²³		X	X	X		X (C2,3,6)			X	
Markers of Bone Turnover and RNA ²⁴	X		X			X(C3,6)			X	

Procedures and Clinic Visits

1. Written informed consent must be obtained within 28 days period prior to Cycle 1 Day 1.
2. Medical history at screening will detail demographic, family history, co-morbidities, prior treatments for prostate cancer and baseline adverse events.
3. Archival tumour tissue will be obtained for molecular characterisation. Patients who do not have archival tumour tissue will be required to have a repeat tumour biopsy in order to obtain the required tumour tissue for histological confirmation and for subsequent molecular characterisation.
4. Fresh tumour biopsies are a mandatory component of this study and will be obtained prior to commencing treatment (during the screening period) and post treatment (at any point from Day 8 to Day 28 of Cycle 1). The third biopsy at the time of treatment discontinuation is optional.
5. At each clinic review, symptoms, concomitant medication, treatment compliance and adverse events will be assessed. Adverse events will be assigned a grade according to the CTCAE version 4.02 and causality. Adverse Event follow-up is required for 30 +/-5 days post last dose of treatment to determine if any new or on-going drug related AE or any SAE regardless of relationship to drug persists.
6. Includes physical examination, blood pressure, heart rate, respiratory rate, oral body temperature, and weight. Height will only be measured at the screening visit. A full physical examination will be performed at screening, Cycle 1 Day 1 and at the EOT visit. At all other clinic reviews physical examinations will be performed as clinically indicated.
7. A Brief Pain Inventory Questionnaire will be given to the patient to fill in at screening and at the beginning of each cycle. The Brief Pain Inventory Score will be annotated in the patients CRF.
8. ECG will only be performed at the screening visit. ECGs should be obtained with the subject in the supine resting position for several minutes. Abnormal ECG related to electrolyte abnormalities should be repeated following the correction of the electrolyte abnormalities. ECGs will only be repeated beyond screening if clinically indicated.
9. A full array of safety bloods including the full blood count, blood chemistry, liver function test, clotting profile, glucose, amylase, etc. will be obtained and checked at the beginning of each cycle of treatment.
10. Serum testosterone level will be checked during the screening period to ensure a systemically castrate state [testosterone levels of < 50 ng/dL (< 2.0 nM)]. Testing for serum testosterone, PSA and routine safety bloods will be performed at the local site laboratory.
11. PSA testing will be done at screening and every 12 weeks while on treatment. PSA responses by PCWG2 criteria will need to be confirmed 4 or more weeks later.
12. Neuron specific enolase and chromogranins A and B to be performed in patients with baseline PSA<10.
13. A bone scan will be obtained at baseline and after every 3rd cycle of treatment. New bone deposits will need to be confirmed with a repeat bone scan 6 or more weeks later.
14. DW-MRI is optional and will be performed at baseline (screening) and every 12 weeks thereafter.
15. CT scan will be obtained at baseline and after every 3 cycles of treatment. If a status of partial or complete response is made, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.
16. Disease progress assessment will be made after every 3rd cycle of treatment at the clinic visits.
17. A buccal swab for DNA analysis should be collected at the indicated time point
18. Saliva for DNA analysis should be collected using an Oragene Kit at the indicated time point
19. Serum plasma for circulating plasma DNA and RNA will be collected at the indicated time points in BD Vacutainer® CPT™ tubes (3x10mls).
20. Blood for CTC analysis should be collected at the indicated time points in 2 Cell Save™ tubes (10mL each, Veridex, PA).
21. Blood samples for whole blood miRNA analysis will be collected at the indicated time points in a 2.5ml PAXgene Blood RNA Tube
22. Blood samples (1x8.5mls) will be collected for PTEN proteomics profiling at the indicated time points.
23. Urine and plasma metabolomics profiles will be evaluated both at baseline and during treatment at the indicated time points. Blood samples (2x6mls) will be collected in a 6ml BD vacutainer with heparin -5min pre dose and 2 hour post dose. A 24 hour urine collection will be collected.
24. Urine collected after the void of the first morning sample will be collected at the indicated timepoints to assess markers of bone turnover such as telopeptides.

Patients should be fasted for 8 hours prior to all blood samples on the days where metabolomic samples are collected (screening, C1D1, C1D8, C2D1, C3D1, C6D1 and EOT).

12 TRIAL TREATMENT

12.1 Drug Manufacturer

Olaparib tablets will be manufactured and provided free of charge by AstraZeneca to participating centres. AstraZeneca will manufacture to Good Manufacturing Practice (GMP) and UK Legislation.

12.2 Presentation / Formulation of Olaparib

Olaparib is presented for oral administration as a green, oval bi-convex film-coated tablet containing 100 mg of drug substance.

12.3 Drug, Dose and Schedule

The dose of 400 mg olaparib, twice daily orally, continuous dosing has been selected for this protocol based on the pharmacokinetic (PK), pharmacodynamic (PD) and clinical efficacy data from the Phase I-II studies including an ongoing bioavailability study (10, 11, 49, 50, 61, 62). The olaparib dose should NOT be adjusted according to the patient's body weight, even for very heavy or light patients. Patients will be given sufficient supplies for 1 cycle (28 days) of treatment. If a patient is not able to attend the clinic review due to a public holiday falling on the 28th day of the cycle or for other unforeseen circumstances consideration should be given to ensure the patient has sufficient drug supplies

Patients should be advised to withhold study drug on the morning of their clinic appointments for trial assessments.

12.4 Instructions for Administration of Olaparib

Patients should swallow the olaparib tablets whole with a glass of water in the morning and evening at the same times each day to ensure a dose interval of approximately 12 hours. All doses should be taken with approximately 240mL of water (1 glass of water) and can be taken with a light meal. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. If vomiting occurs shortly after the olaparib is swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the trial miss a scheduled dose for whatever reason (e.g. as a result of forgetting to take the dose of olaparib), he will be allowed to take the scheduled dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

12.5 Olaparib Treatment Compliance

A member of the Investigative site's study team will query the patient for treatment compliance at day 1 of each new cycle of treatment. All patients must return their bottles of

olaparib at the appropriate scheduled visit, when new bottles will be dispensed. Compliance will be assessed by capsule count and questioning by the study nurse and the information will be recorded.

12.6 Duration of Therapy

Patients may continue with olaparib treatment as long as they remain free from intolerable toxicity, in the Investigator's opinion, are receiving clinical benefit and do not meet any discontinuation criteria (see Section 10.9 for discontinuation criteria).

12.7 Supportive Care Guidelines

Based upon experience from Phase I and II studies, olaparib is generally well tolerated. The safety concerns are primarily related to the risk of myelosuppression. Supportive care should be provided therapeutically and prophylactically as deemed necessary by the treating physician including but not limited to the items outlined below:

Gastrointestinal symptoms

Prophylactic anti-emetics and/or anti-diarrhoeals will not routinely be given. Should a patient develop nausea, vomiting and/or diarrhoea that, in the Investigator's opinion, is considered to be related to olaparib, then appropriate prophylactic treatment may be initiated. Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

Myelosuppression

Routine prophylaxis with granulocyte colony-stimulating factor (G-CSF)/granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin is not recommended. Nevertheless, use is permitted at the Investigator's discretion and according to local hospital guidelines. The occurrence of leukopenia and/or anaemia should be managed as deemed appropriate by the investigator. The use growth factors must be discontinued once the AE has recovered to CTCAE grade 1 or better. They may be resumed, if necessary, if leukopenia/anaemia develops again and discontinued once it recovers. The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the eCRF. Checking haematinics levels (Iron, B12 and folate) and providing supplementation if these are found to be low is advocated. Transfusions may be given as clinically indicated for the treatment of anaemia and thrombocytopenia.

Symptoms Related to Castration

Treatment with androgens, estrogens and progestin to control hot flashes is not allowed. Antidepressants that do not interfere with P450 enzyme function are permitted for the management of hot flashes. Long-term androgen deprivation may lead to metabolic diseases, such as glucose intolerance, hypercholesterolemia, and osteoporosis,

appropriate medication may be prescribed to manage these conditions. All such AEs need to be recorded.

12.8 Guidelines for Management of Toxicity and Dose- Modification

Based on Phase I and Phase II studies, olaparib is generally well tolerated. Safety concerns are mainly related to the possibility of myelosuppression.

Any toxicity observed during the course of the study may be managed by a dose interruption if deemed appropriate by the Investigator. Treatment must be interrupted if any clinically significant NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of olaparib.

Repeat dose interruptions are allowed as required, for a maximum of 42 days on each occasion. Olaparib must be interrupted until the patient recovers completely or the toxicity reverts to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.02) grade 1 or less. When the toxicity is appropriately resolved, the patient can resume treatment with olaparib with a dose reduction according to Table 3 if a treatment break of ≥ 14 days was required for the resolution of the toxicity. If the event recurs with the same severity following olaparib re-challenge, treatment should be interrupted again, and on resolution, a further dose reduction made. A maximum of 3 dose reductions will be allowed. Regular 7-day drug holidays will also be permitted if myelosuppression is an issue at these doses.

If, on re-starting treatment following 3 dose reductions, the event continues to occur at the same severity, treatment should be discontinued and the patient withdrawn from study. If the toxicity has not resolved to at least grade 1 during the maximum 42-day period, and/or the patient has already undergone a maximum of 3 dose reductions already, the patient must permanently discontinue treatment with olaparib. Once the dose of olaparib has been reduced under no account should it be re-escalated.

The dose of olaparib should not be reduced for grade 3-4 gastrointestinal adverse events that have not been adequately managed with appropriate prophylactic measures. In all cases where the olaparib dose has been interrupted or the patient discontinued due to unusual or unusually severe toxicity considered related to olaparib, the Investigator must contact the Chief Investigator and CTSU trial management team. All dose modifications and interruptions (including any missed doses), and the reasons for the modifications/interruptions are to be recorded in the eCRF.

Olaparib should be temporarily withheld in the event of:

- Grade 4 neutropenia
- Grade 2-4 neutropenia with infection
- Platelet count lower than $50 \times 10^9/L$
- Non-haematological toxicity grade 3 or greater, except nausea, vomiting or diarrhoea and fatigue associated with suboptimal pre-medication and/or management OR transient and clinically insignificant biochemical blood results.

- Aspartate transaminase (AST) or alanine transaminase (ALT) elevations grade 3 or higher for more than 7 days.
- New or worsening pulmonary symptoms or radiological abnormality occurs which are suggestive of pneumonitis
- Any other toxicity that, in the view of the principal investigator and the medical monitor, represents a clinically significant hazard to the patient until resolution of toxicity to no more than grade 1.

Standard Dose	Olaparib Dose
First dose reduction due to NCI-CTC grade 3 or 4 treatment-related Serious Adverse Events / Adverse Events (excluding inadequately managed gastrointestinal symptoms)	300 mg BID
Recurrent episode of NCI-CTC grade 3 or 4 event despite one previous dose reduction (excluding inadequately managed gastrointestinal symptoms)	200 mg BID
Recurrent episode of NCI-CTC grade 3 or 4 event despite two previous dose reductions(excluding inadequately managed gastrointestinal symptoms)	100mg BID

Table 3: Summary Guidelines for Dose Reductions

Management of prolonged haematological toxicities including anaemia, neutropenia or thrombocytopenia whilst on study treatment

If any study treatment is interrupted/ delayed because of one or more of the following:

- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 neutropenia
- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 thrombocytopenia
- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 anaemia and or development of blood transfusion dependence

Weekly blood counts should be performed during the study treatment interruption/delay. If the levels have still not recovered to CTC Grade ≤ 1 after 42 days of dose interruption, the patient should be referred to a haematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Bone Marrow or blood cytogenetic analysis:

If a bone marrow analysis is carried out to evaluate cytopenia it should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Development of myelodysplastic syndrome should be reported as an SAE and full reports must be provided.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Chief Investigator and CTSU trial management team. All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded.

12.9 Packaging and Labelling

AstraZeneca have employed Fisher Clinical Services to coordinate IMP packaging, labelling and distribution for this trial. Olaparib will be supplied in High Density Polyethylene containers containing desiccant. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence. Olaparib will be provided to each site in labelled bottles. Each bottle will have a label permanently affixed to the outside and will be labelled in accordance with Good Manufacturing Practice and local regulations, stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. Labels will refer to Olaparib as AZD2281 and will include blank lines for quantity of tablets to be taken, patient trial ID and date of dispensing.

12.10 Drug Storage

Drug Storage by Pharmacy

All study medication must be kept in a secure place under appropriate storage conditions (at temperatures less than 30°C and protected from light). Study medication should not be stored under refrigerated conditions. Additional information is provided in the olaparib Investigator's Brochure. Any deviations from the recommended storage conditions should be immediately reported to the sponsor and the use of olaparib interrupted until authorisation for its continued use has been given by AstraZeneca and the sponsor.

Storage Requirements for the Patient

Olaparib must be stored in the bottle with the cap tightly on at room temperature. Study medication should not be refrigerated. Patients should be advised to keep all medication out of the sight and reach of young children.

12.11 Distribution of Drugs to Site

No drug will be distributed to participating centres unless ICR-CTSU is satisfied that the required approvals, agreements and initiation procedures are complete.

Participating pharmacy departments should contact Fisher Clinical Services via the ICR-CTSU trial management team to request drug supplies following patient registration.

Records must be kept for all deliveries and a copy of the order / delivery note placed in the Site Pharmacy File and kept within the pharmacy department as in routine practice. At the end of the trial, it must be possible to reconcile supply and usage of all stock. Account must be given to any discrepancies and certificates of delivery and return must be signed.

12.12 Pharmacy Responsibilities and Drug Accountability

Labelling:

Labelling will be the responsibility of Fisher Clinical Services and will be compliant with Annex 13 of the Good Manufacturing Guidelines (GMP) and all applicable local regulatory requirement. Each hospital pharmacist must also insert the name of the Principal Investigator (PI) or hospital specific code by which the PI can be identified, together with the Trial ID and patient's name,.

The local pharmacy department must designate a responsible person for ensuring that:

- The study drug is handled and stored safely and properly
- The study drug is labelled for each patient in accordance with Annex 13 of the EU Good Manufacturing Practice (GMP) Guidelines
- The study drug is dispensed only to trial patients and in accordance with the protocol and under the guidelines of the site's dispensing standard operating procedure
- Full accountability is maintained for the study drug
- Patients should be instructed to return unused olaparib, preferably in their original packs. Olaparib which has been dispensed to a patient and returned unused must not be re dispensed to a different patient
- There is a sufficient supply of study drug for patients' continued treatment, and in a timely manner, contact ICR-CTSU for re-supply of stock
- Study drug expiry dates are monitored and are used in order of expiry date order i.e. earliest expiry first
- All unused drugs will be accounted for and retained until advised otherwise. Unused and returned study drug may be destroyed locally in accordance with hospital protocol and following written instructions from the sponsor

Patient cards

Small wallet sized cards will be produced by ICR-CTSU on request by the participating centre. Each card will state:

- the name of the participating centre
- that the patient is participating in the TOPARP trial
- that the patient is taking olaparib

12.13 Concurrent Medications

The concurrent administration of other anticancer therapies, including cytotoxic, hormonal (except LHRH analogues) or immunotherapy, is prohibited during study treatment. The use of any natural/herbal products or other “folk remedies” should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded.

Olaparib is an investigational drug for which no data on *in vivo* interactions are currently available. Based on *in vitro* data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. *In vitro* data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib. Whilst this is not an exhaustive list of inhibitors, it covers the known potent inhibitors which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfanavir

For patients taking any of the above, the required wash-out periods prior to starting olaparib is one week.

In addition, to avoid potential reductions in exposure due to drug interactions, the exclusion of the following P450 inducers is recommended:

- Phenytoin, rifampicin, rifapentin, reifabutin, carbamazepine and phenobarbitone, nevirapine, modafinil and St John’s Wort (*Hypericum perforatum*)
- For patients taking any of the above, the required wash-out periods prior to commencing olaparib are:
- Phenobarbitone - 5 weeks; any of the others - 3 weeks.

If use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient’s safety and welfare, the Investigator must contact the ICR-CTSU and a decision to

allow the patient to be enrolled in the study will be made on a case-by-case basis by the Chief Investigator.

If at any time an investigator suspects a drug-drug interaction due to olaparib, an AE report should be completed and the study sponsor informed.

Permitted Concomitant Therapy

- Leuteinizing hormone-releasing hormone (LHRH) agonists to maintain a testosterone level <50g/dL should be administered in patients who have not undergone an orchidectomy.
- Conventional multi-vitamins and minerals.
- Stable chronic non-immunosuppressive systemic doses of corticosteroids up to a dose of prednisolone 5mg BID or equivalent so long as the treatment was initiated prior to commencing the trial medication with evidence of progression on the dose of steroids. Higher doses of steroids are permitted if clinically indicated for acute medical conditions.
- Initiating bisphosphonate therapy or adjusting bisphosphonate dose/regimen within 30 days prior to Cycle 1 Day 1 is prohibited. Patients on a stable bisphosphonate regimen are eligible and may continue.
- Anticoagulant Therapy: Patients who are taking warfarin may participate in this trial however, it is recommended that prothrombin time (International Normalised Ratio [INR] and activated partial thromboplastin time [APTT]) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted and is preferable given the potential for myelosuppression.
- **Palliative radiotherapy:** may be used for treatment of pain at the site of bony metastases that were present at baseline, providing the Investigator does not feel that this is an indication for the patient to come off treatment due to disease progression. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the eCRF.

Therapy considered necessary for the subject's welfare and which is believed not to interfere with the study medication may be given at the discretion of the investigator. If concurrent medications may have an effect on study outcomes, a statement to the effect that these medications should be administered in dosages that remain constant throughout the course of the trial should be included. All medications (prescriptions or over-the-counter medications), the reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records.

13 PHARMACOVIGILANCE

13.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a study drug, whether or not considered related to the study drug.

Adverse Reaction (AR): all untoward and unintended responses to the study drug related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions i.e. an AR is possibly, probably or definitely related to the study drug. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR): Any untoward medical occurrence or effect which occurs from screening until 30 days after the last dose of study drug:

- **results in death:** the patient's death is suspected as being a direct outcome of the AE.
- **is life-threatening:** refers to an event in which the subject was at risk of death at the time of the event. It also refers to an event that would result in death with the continued use of the product; it does not refer to an event which hypothetically might have caused death if it were more severe.
- **requires hospitalisation, or prolongation of existing inpatient hospitalisation:** admission to hospital overnight or prolongation of a stay in hospital was necessary as a result of the AE..
- **results in persistent or significant disability or incapacity:** the AE results in a significant or persistent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- **results in a congenital anomaly or birth defect**

Hospitalisation meeting the definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Inpatient admission does not include: rehabilitation facilities, hospice facilities, skilled nursing facilities, nursing homes, routine emergency room admissions, same day surgeries (as outpatient/same day/ambulatory procedures), or social admission (e.g., subject has no place to sleep). Outpatient treatment in an emergency room is not itself an SAE, although the reasons for it may be. Hospital admissions/surgical procedures planned for a pre-existing condition before a patient is randomised to the study are not considered SAEs, unless the illness/disease deteriorates in an unexpected way during the study

Medical judgement should be exercised in deciding whether other AE/ARs are serious. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious

N.B. progressive disease and death due to disease are not considered SAEs but should be reported on the relevant forms.

Suspected Unexpected Serious Adverse Reaction (SUSAR): Any serious adverse event with a suspected relationship to study drug that is not listed on the Investigator Brochure (IB) and in the opinion of the Chief Investigator, is unexpected.

13.2 Clinical & Laboratory Adverse Events

AEs Based on Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

AEs Based on Examinations & Laboratory Tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfil any of the SAE criteria or are the reason for stopping treatment with the investigational product. If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator should use the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value).

The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms.
- Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting as an AE).
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy.
- Test result leads to any of the outcomes included in the definition of a SAE.
- Test result is considered to be an adverse event by the investigator or sponsor.

- Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for bullet point 4.
- Relevant clinically significant laboratory results should be recorded in the patient's eCRF.

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the sponsor (or his/her designated representative), or until a diagnosis that explains them is made.

13.3 Causality

Many adverse events that occur in this trial, whether they are serious or not, will be known treatment related toxicities. The Principal Investigator is responsible for the assessment of causality of serious adverse events (see definitions of causality table).

If there is any doubt about the causality of an event, the investigator should inform ICR-CTSU who will notify the Chief Investigator. The drug manufacturer and/or other clinicians may also be asked for advice.

13.4 Severity of Adverse and Serious Adverse Events

Adverse event (AE) severity is a clinical determination of the intensity of an AE and SAEs. The severity assessment for a clinical AE should be completed using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.02). Any AE not listed in the CTCAE will be graded as follows:

Table 4: Severity of Event

Grade	Definition	Description
1	Mild adverse event	Does not interfere with the patient's usual function [awareness of symptoms or signs, but easily tolerated (acceptable)].
2	Moderate adverse event	Interferes to some extent with the patient's usual function [enough discomfort to interfere with the usual activity (disturbing)].
3	Severe and undesirable adverse event	Interferes significantly with the patient's usual function [incapacity to work or to do usual activities (unacceptable)].
4	Life-threatening or disabling adverse event	Results in risk of death, organ damage or permanent disability (unacceptable).

5	Death related to adverse event. Relationship to Study Drug	Event has a fatal outcome.
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Causality of Event

A determination should be made by the investigator regarding the relationship (if any) between an AE and the study drug. A causal relationship is present if there is a reasonable possibility that the AE may have been caused by the study drug. The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study.

Table 5: Definitions for Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

The expectedness of a SAR related to the study drug should be assessed by the Chief Investigator in accordance with the information provided in the IB for olaparib.

Expected SARs should be reported as per the SAE reporting guidelines. SAEs should be reported up to 30 days after the patient's last dose of study medication

A summary of 'expected' adverse reactions as stated in the IB is listed below:

Table 6: Expected Adverse Reactions (Olaparib Monotherapy)

Frequency of Adverse Events	Very common	Common	Rare
Grade (G)	Mild to moderate CTCAE:G1-2	Mild to moderate CTCAE:G1-2	Mild to moderate CTCAE:G1-2

Adverse Events	Nausea	Anaemia	Lymphopenia
	Vomiting	Headache	Tachycardia
	Fatigue	Dyspepsia	Thrombocytopenia
		Dizziness	Neutropenia
		Asthenia	
		Decreased appetite	
		Dysgeusia	
		Constipation	

13.5 Procedures for Recording and Reporting Adverse Events

13.5.1 Reporting Serious Adverse Events (SAEs) to ICR-CTSUS

Any SAE that occurs from the time of screening and up to 30 days following the last dose of olaparib must be reported, whether or not considered causally related to the study treatment. For patients that do not enter the trial SAEs should be reported from screening until a decision is made the patient will not enter the trial. Any SAEs reported in this period should be followed until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised

All SAEs should be reported to ICR-CTSUS, within 24 hours of the study team becoming aware of the event, by completing the trial specific SAE forms and faxing to:

The ICR-CTSUS safety desk
Fax no: 0208 722 4368
For the attention of the TOPARP Trial team

Investigators or other site personnel must ensure that:

- All SAE forms must be completed, signed and dated by the Principal Investigator or designated representative.
- All SAE reports are supported by documentation in the patient's medical records. Obtain and maintain in his files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
- All patients with a serious adverse event must be followed up and the outcomes reported in a follow up severe adverse event report form to the ICR CTSUS.
- In the event of fatal or life-threatening AEs where important or relevant information is missing, active follow-up must undertaken immediately.

13.6 Review of Serious Adverse Events (SAEs) or Reactions (SARs)

Reported events / reactions using the SAE forms will be assessed by the Chief Investigator (or designated representative) for causality and expectedness.

NB. The Chief Investigator cannot down grade the Principal Investigator's assessment of causality.

SAEs assessed as having a causal relationship to study drug and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities by ICR-CTSU (see figure 4 for SAE reporting).

Centres should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of the SAE.

13.7 Expedited Reporting of SUSARs

If an SAE is identified as being a SUSAR by the Chief Investigator, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Main REC, the sponsor institutions and AstraZeneca within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the Chief Investigator, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Main REC, the sponsor institutions and AstraZeneca within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA, Main REC, the sponsor institutions and AstraZeneca as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

The Principal Investigators at all actively recruiting centres will be informed of any SUSARs occurring within the trial at regular intervals.

13.8 Follow up of Serious Adverse Events

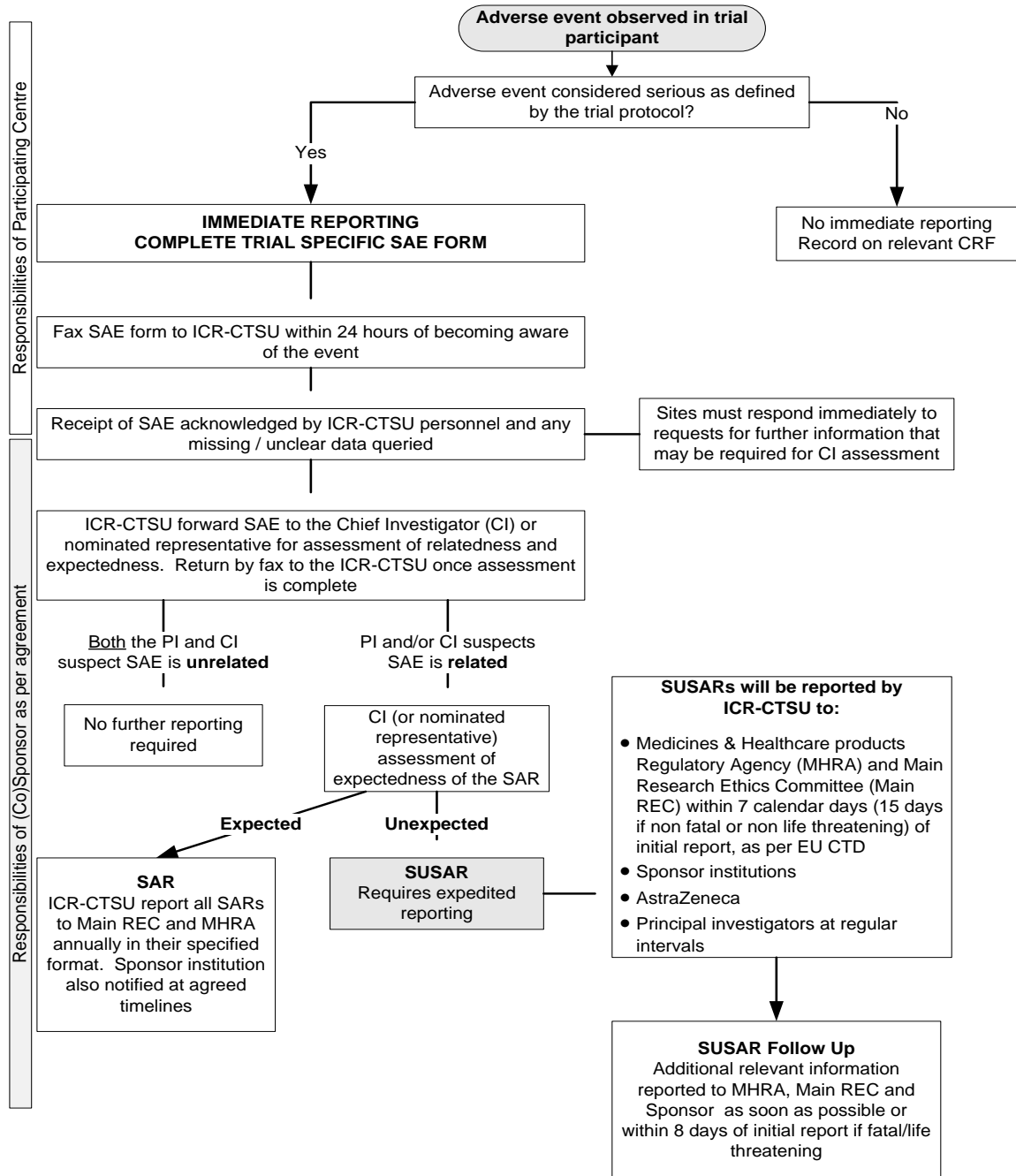
Centres should continue to follow up SAEs until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Information on outcome of the SAE should be completed on the relevant part of the original SAE and faxed to ICR-CTSU as soon as the Principal Investigator becomes aware.

NB Any male patient who fathers a child whilst on study medication must be followed up and the outcome reported to ICR-CTSU who will then forward the details to AstraZeneca.

13.9 Annual Reporting of Serious Adverse Reactions

An annual report will be provided to the MHRA and the Main REC, by ICR-CTSU and copied to the Co-sponsors, on the anniversary of the date when the Clinical Trials Authorisation (CTA) was obtained. This will include all related events reported on SAE forms, and a report from the Independent Data Monitoring Committee (IDMC).

Figure 4: Flow diagram for SAE reporting, and action following report



NB. All SAE's should continue to be followed up as specified in the protocol.

14 STATISTICAL CONSIDERATIONS

14.1 Trial Design

The aim of this design is to look for potentially sensitive subgroups of patients by undertaking a screening trial (part A) followed by a validation trial (part B) if there is evidence a sensitive subgroup exists.

Both of these trials are non-randomised with response rate being assessed at 6 months post registration as the primary endpoint. These trials will be followed by a randomised phase II trial (part C) in the sensitive patient groups with overall survival as the primary endpoint. The aim is to identify a sensitive subgroup with a 50% response rate on the basis that high response rates are necessary to be confident of demonstrating a survival benefit, the primary goal of the phase II strategy.

It is possible that all patients are sensitive to treatment in which case it has to be possible to apply the same efficacy and inefficacy criteria as are used in the validation trial to all patients in the screening trial.

Part A

The screening trial will involve all comers (unselected patients) and is an open-labelled, multi-centre two-stage design based on $H_0: p_0=0.05$; $H_a: p_1=0.20$; $\alpha=0.02$ and $\beta=0.10$. It will recruit a **maximum of 45 patients** (30 in stage 1 and 15 in stage 2) with an initial efficacy level of 20% and an inefficacy level of 5%, to allow for the fact that only a small subset of patients may be sensitive to olaparib.

This part will evaluate the anti-tumour activity of olaparib in unselected CRPC patients and will identify potential biomarkers of response.

- **Stage 1**

The first stage will enrol 30 patients and when all 30 have been followed up for a minimum of 6 months an interim analysis will take place to evaluate the response rate:

Given the efficacy level of 20% and inefficacy level of 5% the trial will be terminated with the conclusion of inefficacy if there are **2 or fewer responses**. If there are **15 or more responses** in the first stage, broad efficacy will be concluded and no more patients will be entered and Part C will commence in unselected patients.

If between **3 to 14 patients respond**, patient accrual will continue to a total of 45 patients (stage 2) and an investigation into the identification of a potential biomarker of response will be carried out.

- **Stage 2**

If the trial progresses to stage 2, a further 15 patients will be recruited, giving a total of 45 patients for part A. An interim analysis will be triggered once 45 patients have been followed up for a minimum of 6 months or alternatively we observe 23 or more responses. The recruitment will be halted.

If **23 or more** patients respond, Part C will be initiated. If **5 or fewer patients** respond, the null hypothesis will be accepted and the study will be terminated. If **between 6 and 22 patients respond**, an investigation into the identification of potential biomarkers of response will be carried out. If a potential biomarker subgroup is found, Part B will be undertaken. If a subgroup is not found, then Part C will be undertaken if at least 19 of the patients have responded, otherwise the study will be terminated since sufficient activity has not been observed based on $H_0: p_0=0.3$; H_a ; $p_1=0.5$; $\alpha=0.059$ and $\beta=0.11$.

Deriving a classifier for identification of tumours with high susceptibility to PARPi olaparib in CRPC.

All patients participating in this trial will have their archival tissue, fresh tumour biopsies and circulating tumour cells collected prior to starting olaparib. The primary biomarkers to be evaluated include PTEN loss by IHC and FISH, *ETS* gene rearrangements by FISH and RAD51 foci formation. It should be noted that PTEN loss and *ETS* rearrangements co-associate and are found in approximately 50% of prostate cancers. In addition that is emerging evidence to suggest that RAD51 foci formation is diminished in tumours with HR defects such as those with loss of PTEN and *ETS* rearrangements (15, 27, 41, 44).

See section 2.1 for a discussion of relevant biomarkers.

Biomarkers will be classified as either established markers of sensitivity to synthetic lethality with PARPi (e.g. *BRAC1* -/-, *BRAC2* -/-), or as exploratory biomarkers. Established biomarkers will have a guaranteed place in the biomarker classifier but exploratory biomarkers will have to be shown to have predictive ability from the trial data.

The correlation between biomarkers will first be examined using Spearman's rank correlation. If two biomarkers are highly correlated or known to be highly correlated from previous evidence one of the biomarkers will be dropped. The use of appropriate cut-points of continuous scores for individual biomarkers will be decided before examining their association with response.

For potential promotion to the classifier, a false discovery rate of 10% or less will be applied to all exploratory biomarkers, using the p-values from the univariate association with response (Fisher's exact test, $p < 0.10$ 2-sided). If evidence exists from other sources it may be incorporated into the assessment of specific biomarkers using meta-analysis to give an 'overall' p-value.

Secondly, identification of a multivariable predictive classifier will be undertaken using a significance level of 10% or less for the inclusion of the biomarker in the classifier (logistic

regression). In the event of a tie, e.g. two or more classifiers with similar performance, a liberal approach will be adopted on the basis that it will be possible to exclude non-responsive biomarker groups at a later date. Standard prognostic factors may be included in the classifier if they are independent of the biomarkers.

The goal will be to develop a classifier which identifies a group with a response rate of 40% or more on the basis that the levels for inefficacy and efficacy are set at 30% and 50% respectively.

The biomarker defined subgroup satisfying the above criteria will be selected for validation in Part B. If olaparib successfully graduates from this, stage Part C will be undertaken. If convincing evidence arises from other translational studies of olaparib or other PARP inhibitors the IDMC will be asked to advise whether or not an analysis should take place.

Part B

The biomarker status of patients registered in Part B will be evaluated and only patients with the presence of the putative biomarker subgroup identified in Part A will be entered. Forty-four additional patients will be treated in this single stage, which assumes $H_0: p_0=0.3$; H_a ; $p_1=0.5$; $\alpha=0.05$ and $\beta=0.15$.

If **19 or more** of the **44 patients** respond (43%), then a proposal for a subsequent randomised controlled trial to investigate the predictive potential of the biomarker will be developed. If **18 or less** patients respond, the study will be terminated.

Further information regarding the sample size calculations of both parts A and B is shown in Appendix A. The detectable effects in the biomarker sensitive group assuming 80% power are presented on Appendix B.

14.2 Analysis populations

Analysis populations are defined as follows:

- **Intention to treat (ITT):** This population includes all patients enrolled into the study regardless of whether they are later found to be ineligible, a protocol violator, never treated or not evaluated. Patients for whom the primary endpoint cannot be evaluated will be treated as non-responders.
- **Evaluable-patient population:** This population contains all enrolled patients for whom the primary endpoint can be evaluated. A patient will be “evaluable” if **at least a bone scan or RECIST measurement is available. Where evaluability is difficult to define the final decision will rest with the IDMC.**
- **Per protocol (PP):** This population contains all enrolled patients who received at least 1 cycle of olaparib without major protocol violations.
- **Safety population:** This population includes all enrolled patients who received at least 1 dose of olaparib.

The analysis of the primary outcome will use the evaluable-patient population with sensitivity analyses in the ITT and per protocol populations. All other analyses will use the ITT

population. The ITT and PP analyses will treat non-evaluable patients as non-responders. The safety population will be used to further characterise the safety profile of olaparib in advanced CRPC patients.

14.3 Primary Efficacy Endpoint

Response will be defined by:

- Objective response by modified RECIST (baseline lymph node size must be ≥ 2 cm to be considered a target lesion) (Appendix E) and / or
- Conversion of circulating tumour cell count (CTC) to $< 5/7.5$ ml blood nadir confirmed by at least two readings 4 weeks apart and / or
- PSA decline of $\geq 50\%$ (according to the PCWG2) (Appendix D)

Failure will be defined as:

- Progression by RECIST- increase in measurable lesion size(S) or new lesion AND/OR
- Progression by bone scan – see Appendix D

Response will be evaluated 6 months post registration. The last value of PSA, CTC count, CT scan and bone scan on or up to four weeks before the date of first study treatment will be used as the baseline value for this assessment. The response rate will be presented along with its exact two-sided 95% confidence interval.

14.4 Secondary Efficacy Endpoints

The following endpoints will be assessed 6 months post registration. However, decisions made within the trial to comply with the adaptive design will not necessarily require 6 months follow up on all patients, e.g. it may be possible to enter patients into the second stage of Part A when it is clear between 3 and 14 responses will occur in the first stage even though not all 30 patients have 6 months follow up.

PSA response and PSA progression are defined according to the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA value from cycle1 day 1 (baseline). This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. The first PSA reading will be obtained at week 12.

Time-to-PSA Progression

For patients who have achieved a $\geq 50\%$ decrease from the cycle 1 day1 (baseline), the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the **nadir** is documented. This must be confirmed by a second consecutive value obtained 4 or more weeks later. For patients without a PSA decrease of this magnitude or no decrease at all, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the **baseline** is documented. This must also be confirmed by a second consecutive value 4 or more weeks later. Time to PSA progression will be summarised using Kaplan-Meier methods.

Duration of PSA response

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the cycle 1 day 1 (baseline) value (must be confirmed by a second value) until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be assessed at the last PSA measurement. Duration of PSA response will be summarised by the median and presented along its 95% confidence interval.

PSA objective response rate (PSA-ORR)

The proportion of patients having achieved partial or complete response defined by PSA will be reported with the corresponding exact two-sided 95% confidence interval.

Pattern of PSA Responses

Waterfall plots will be presented (as per PCWG2 recommendations) that show the percentage of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy), as well as the maximum decline in PSA that occurs at any point after treatment. Waterfall plots provide a broader display of PSA changes than dichotomised responses.

CTC Response

The proportion of patients with a CTC conversion to $<5/7.5$ ml blood at nadir (confirmed by two readings at least 4 weeks apart) will be presented along an exact two-sided 95% confidence interval. Its association with PFS and OS will be examined via Cox regression models first univariately and subsequently in a multivariable model adjusting for potential confounders. Waterfall plots of CTC falls will also be presented that show the percentage change in CTC counts from baseline to 12 weeks as well as maximal CTC count declines that occur at any point after treatment.

The following endpoints will be evaluated using Kaplan and Meier methods:

Radiographic Progression Free Survival (rPFS)

Radiographic progression free survival (rPFS) will be defined by either RECIST progression and /or progression on bone scan (Appendix D and E). It will be measured from the date of trial entry to the first occurrence of radiographic progression or death from any cause. If no event exists, then rPFS will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Time to Radiographic Progression

Time to radiographic progression (progression defined by either RECIST progression and /or progression on bone scan) will be measured from the date of trial entry to the first occurrence of radiographic progression. Death from prostate cancer or any other cause without prior radiographic evidence of progression will not count as an event. If no event exists, then time to radiographic progression will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Progression Free Survival (PFS)

Progression free survival will be measured from the date of trial entry until radiographic progression, unequivocal clinical progression or death. If no event exists, then PFS will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Overall Survival (OS)

OS will be measured from the date of trial entry to the date of death (whatever the cause). Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow-up.

14.5 Tertiary/exploratory Endpoints

- **Pain palliation:**

Pain palliation will be assessed using the Brief Pain Inventory's (BPI Short Form) worst pain intensity score and average score. A composite of the four pain items (worst, least, average, right now) will be presented as supplemental information. Change in BPI score from baseline will be assessed at 6 months post registration. A reduction of two points in the worst pain score relates to an improvement of pain. The analgesic relief received will be described.

- **Safety Endpoint**

Safety analysis will be summarised using the safety population. Extent of exposure to study drug will be summarised and details will be provided. Treatment emergent adverse

events (AEs) are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose. Adverse events will be graded according to the NCI-CTCAE v4.02. Adverse events will be summarised by grade, according to the worst grade experienced. In addition, most frequently observed AEs will be summarised. In the summary of AE, an AE occurs more than once within a SOC and PT will be counted only once using the worst grade experienced. Serious AE and deaths observed within 30 days of the last dose of study treatment will be provided in a listing.

All adverse events resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of study drug will also be listed and tabulated by preferred term. Clinical laboratory test results will be collected pre-treatment and through 30 days post last dose of study treatment. All laboratory test results will be classified according to the NCI CTCAE v4.02 criteria. Standard reference ranges will be used for missing or discrepant normal ranges. Baseline laboratory test values are the results from the last blood samples drawn on or prior to the first day of study treatment. On-study laboratory test values are those results from blood samples drawn a day after the first study treatment up until 30 days after the last dose of study treatment.

- **Impact of treatment with olaparib on bone metastases imaging by DW-MRI.**

Diffusion-weighted MRI scan will be offered to patients recruited in part A and we expect approximately 50% acceptance rate. This analysis will be **purely exploratory** and we will examine whether response to olaparib expressed by changes in apparent diffusion coefficients produced by the DW-MRI scan correlate with 1) PSA decline, 2) CTC conversion and 3) radiological responses coming from conventional imaging. In 20 patients it is possible to detect a correlation coefficient of 0.6 which is equivalent to the parameter explaining 36% of the variation using a 2-sided 5% significance level.

14.6 Data Monitoring

An Independent Data Monitoring Committee will meet in confidence at regular intervals, firstly to review the safety analysis following the first 5 and 10 patients recruited and subsequently every 6 months (or at intervals determined by them) to review accrual, safety and efficacy data.

The replacement of patients who withdraw from the study or who are un-evaluable for reasons deemed not to be treatment related will be based on the advice of the committee. The committee will review the results of each interim analysis (progression from stage 1 to stage 2 and progression to part B) and will be asked to advise. For completeness a sensitivity analysis of the progression free rate calculated by the Kaplan Meier product limit method will also be presented in which withdrawals and deaths are censored. The summary statistic will be the progression free rate at 6 months together with its 95% one-sided confidence interval.

15 TRANSLATIONAL RESEARCH

Paraffin embedded tumour blocks or unstained sections from archival tumour tissue from the time of the original diagnosis or from a biopsy / resection of metastatic disease will be required from all subjects who enrol on the study. Patients who do not have adequate archival tumour tissue will be required to have tumour confirmed in a repeat tumour biopsy in order to be enrolled on the study. CTCs, urine, plasma samples and mandatory fresh tumour biopsies will be obtained at various time points during the study (Table 2 & 7). CTCs will be enumerated to evaluate conversion rates (CTC from ≥ 5 cells/7.5ml blood at baseline to < 5 cells/7.5mls) on this treatment. The tumour tissue will be assessed for multiple biomarkers including *PTEN* and *ERG* expression, *PTEN* deletions, *TMPRSS2-ETS* gene rearrangements using multicolour FISH studies, markers of DNA damage and HR repair such as γ H2AX and RAD51 focus formation, markers of tumour cell proliferation and cell cycle phase. Blood samples for plasma-based biomarker will be utilised for several studies including obtaining normal germline DNA and circulating tumour DNA for mutational analysis (e.g. *BRCA1*, *BRCA2*, *CHEK2*, etc.), quantitative real time polymerase chain reaction for *ERG* detection, proteomics, metabolomics, RNA and microRNA (miRNA) studies. Urine samples will be utilised to evaluate metabolomics, RNA and urine telopeptides profiles. Additional putative predictive biomarkers involved in the HR DNA repair pathway and sensitivity to PARP inhibition may be evaluated to facilitate the characterisation optimal determinants of response and resistance to olaparib treatment. Some of these additional markers/studies may come from other translational studies.

All the tumour tissue, CTC, plasma and urine samples will be sent to the Institute of Cancer Research Biomarker Group for processing and analysis. Some of these samples may be labelled with the patients' initials, hospital pathology number and trial number when they are sent to the research laboratory. When they arrive at the laboratory each sample will be coded with a unique anonymised number and any personal details removed. The number generated is linked to the patient trial ID held at the ICR CTSU. This coding system will maintain patient confidentiality whilst allowing biological details to be compared to treatment findings.

Samples will be stored in a secure area in the Cancer Biomarkers Laboratory at the Institute of Cancer Research. Samples will only be accessible by accredited staff involved in the processing and analysis of the samples. Some of the tumour/plasma samples collected may need to be sent to another site for processing and analysis. This will only occur following an established agreement being set up and assurance that patient confidentiality is maintained. **Instructions for the sample requirements, collection, handling, labelling, shipment and storage will be provided in a reference TOPARP Laboratory Manual for Investigators.**

In some cases the archival tumour blocks will be returned to the local laboratories after the study is complete, depending on local practice. Patients participating on this study will be asked to give permission for possible future research into prostate cancer using these samples. The confidential nature of the tissue and associated data will be fully protected, and any other research using your tissue will first be reviewed and approved by an ethics committee.

These tumour and plasma samples may be used for, but not restricted to, the elucidation of mechanism of response, understanding the mode of action of olaparib and improving the understanding of disease progression.

15.1 Archival Tumour Blocks and Fresh Biopsies

An adequately sized (minimum of 2 mm x 2 mm) archival tumour tissue paraffin block from resection or a core biopsy from the time of the original diagnosis or from a biopsy / resection of metastatic disease at any time prior to study entry is required. Alternatively, unstained slides prepared from the block can be provided. Mandatory fresh biopsies should be obtained at baseline (during the screening period; anytime between Day-28 to Day1), post commencement of treatment (during Cycle 1; anytime between Day 8 and Day 28) and at study discontinuation. The third biopsy is optional and will be obtained at any point between the patient coming off study treatment to the end of treatment visit.

The fresh tumour biopsy may be obtained from either the prostate or a metastatic site that is safe and amendable to a biopsy. Tumour biopsies may be obtained from the prostate itself (if it has not been surgically resected and has not been treated with radiotherapy) via an ultrasound-guided transrectal biopsy. Local recommendations for the procedure will be followed. Alternative sites where a biopsy can be obtained include lymph nodes, bone or liver where there is evidence of cancer on imaging. Patients who do not have evidence of visceral disease but do have evidence of bone metastasis on the bone scan may undergo a bone biopsy and possible aspirate from the ischium. Ideally, the pre- and post-treatment biopsies will be from the same site.. Refer to the TOPARP Laboratory Manual for specific details on sample collection, handling, storage and shipping requirements.

15.2 Circulating Tumour Cell (CTC) Assessments

A total of 18 blood samples will be drawn over 9 study visits for each patient enrolled during the first 12 months of treatment. Baseline samples will be collected at screening and one Cycle 1 Day 1 and subsequently CTC blood samples will be collected at Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, every third cycle thereafter and at time of discontinuation of study treatment. CTCs will be enumerated using Veridex CellSearch™ platform.. CTC samples in all patients will be used to enumerate CTC counts and evaluate the molecular profile of tumour cells. Refer to the TOPARP Laboratory Manual for specific details on sample collection, handling, storage and shipping requirements. Amongst the molecular markers that will be studied include:

Immunofluorescence: PTEN, ERG, RAD51, γ H2AX and markers of tumour cell proliferation and cell cycle phase.

FISH: Including *PTEN*, *TMPSS2/ERG*

15.3 Plasma and Urine-Based Biomarkers

Plasma and urine samples for different analyses will be collected at multiple time points during the study (refer to Table 7 for details on the specific samples). These samples will be utilised for the purpose of analysing circulating plasma biomarkers including circulating tumour DNA and RNA for mutational analyses, quantitative real time polymerase chain reaction of ERG detection, plasma proteomic signature, plasma and urine metabolomic studies and microRNA (mirRNA) profiles. Proteomic, metabolomic and miRNA profiling may generate signatures that can be used as predictive, prognostic and pharmacodynamic biomarkers that may also be correlated with other study endpoints. Refer to the TOPARP Laboratory Manual for specific details on sample collection, handling, storage and shipping requirements.

Plasma

- **Plasma Metabolomic Profiling:** Blood samples will be obtained at screening, on Cycle 1 Day 1 (-5 min pre-dose and 2hour post-dose), Cycle 1 Day 8 (-5min pre-dose and 2hour post-dose), Day 1 of cycles 2, 3 and 6 (-5 min pre-dose and 2hour post-dose) and at either treatment discontinuation or end of treatment. Patients will be required to fast for at least 8 hours before providing these metabolomic blood samples. During the fasting period water or tea without milk and sugar will be allowed in moderate amounts. For patients who are unable to fast (e.g. insulin dependent diabetic patients) samples should have all these samples consistently collected in a non-fasted state. Whenever possible patients should be seen first thing in the morning to limit the burden of fasting. After the blood draw patients will be permitted to have a light breakfast.
- **PAXgene miRNAs Analyses:** Whole blood samples will be collected at screening, Cycle 1 Day 1, and Day 1 of cycles 3 and 5 and at either treatment discontinuation or the end of treatment visit.
- **Plasma Proteomic profiling:** Plasma samples will be obtained at screening, Cycle 1 Day 1 (pre-dose) and at either treatment discontinuation or the end of treatment visit.
- **Circulating Plasma DNA and RNA:** Plasma samples will be collected at screening, Cycle1 Day 1, Cycle 1 Day 8 and on Day 1 of Cycles 2, 3, 5 and at either treatment discontinuation or the end of treatment visit.

Urine

- **Urine Markers of Bone Turnover (telopeptides):** A urine sample collected after the void of the first morning sample will be collected at screening, Day 1 of cycles 1, 3, 6 and at either treatment discontinuation or the end of treatment visit.
- **Urine Metabolomic Profiling:** 24 hour urine samples will be collected at screening, Cycle 1 Day 1, Cycle 1 Day 8 and on Day 1 of Cycles 2, 3 and 6 and at either treatment discontinuation or the end of treatment visit.

The 24 hour urine sample will be collected from the second urine of the previous day until the first urine of the clinic visit day. The urine sample for markers of bone turnover will be collected at the second urine of the clinic visit day.

15.4 Buccal Swabs

A buccal swab will be collected at screening.

15.5 Saliva Collection

A saliva sample will be collected at screening.

15.6 Diffusion-weighted MRI

Diffusion-weighted MRI (DW-MRI) will be performed on an optional basis in a subset of patients. DW-MRI provides better visualisation of tumour cellularity and the results of DW-MRI will be correlated with bone scan results, PSA, CTC counts and patient outcome.

15.7 Rationale of translational research

The intent of the biomarker / translational research embedded in this protocol is outlined below:

- To characterise the molecular profile of prostate cancer and sub-divide this heterogeneous disease.
- To develop predictive biomarkers of olaparib sensitivity which may be utilised to optimise patient selection for future studies
- To correlate the molecular profile of prostate cancer (in particular but not exclusively *PTEN*, *ERG* status by both IHC and FISH analysis) with clinical outcome
- To determine target modulation from olaparib treatment by the generation of γ H2AX foci formation, a marker of DNA damage in fresh biopsies and CTCs
- To evaluate the utility of early changes to CTC counts as a surrogate of clinical benefit to PARP inhibitors in CRPC
- To correlate CTC changes with PSA and radiological responses to olaparib treatment in CRP.

TIME POINTS	BLOOD BASED BIOMARKERS							URINE BIOMARKERS	
	Saliva	Buccal Swab	CTC	Plasma DNA & RNA Analyses	PAXgene miRNA	Plasma Proteomic Profile	Plasma Metabolomic Profiling (pre and post dose)	Urine Metabolomic profiling	Bone markers of turnover
Screening	X	X	2x10mls	3x10mls	1x2.5mls	1x8.5mls	2x6mls	24 urine collection	Urine collected after the void of the first morning sample
Cycle 1 day 1			2x10mls	3x10mls	1x2.5mls	1x8.5mls	2x6mls	24 urine collection	Urine collected after the void of the first morning sample
Cycle 1 day 8			2x10mls	3x10mls			2x6mls	24 urine collection	
Cycle 1 day 15			2x10mls						
Cycle 2 day1			2x10mls	3x10mls			2x 6mls	24 urine collection	
Cycle 3 day1			2x10mls	3x10mls	1x2.5mls		2x6mls	24 urine collection	Urine collected after the void of the first morning sample
Cycle 4day1			2x10mls						
Cycle 5 day1				3x10mls	1x2.5mls				
Cycle 6 day1							2x6mls	24 urine collection	Urine collected after the void of the first morning sample
Cycle 7day1 & every 3rd cycle thereafter			2x10mls						
End of Treatment Visit			2x10mls	3x10mls	1x2.5mls	1xmls	2x6mls	24 urine collection	Urine collected after the void of the first morning sample

Table 7: Summary of the blood and urine-based biomarker samples for the translational research

For total volumes of safety and research bloods refer to Appendix J

16 TRIAL MANAGEMENT

The trial will be coordinated by ICR-CTSU in accordance with their quality management system.

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, Co-investigators and identified collaborators, the Trial Statistician and the Trial Managers. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of centres and professional groups. Notwithstanding the legal obligations of the Co-Sponsors and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. Where possible, membership will include a lay/consumer representative. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and will include an independent Chairman (not involved directly in the trial other than as a member of the TSC) and not less than two other independent members. It is the role of the TSC to monitor progress of the trial and to ensure there is adherence to the protocol and the principles of Good Clinical Practice. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16.3 Independent Data Monitoring Committee (IDMC)

An IDMC will be instigated to monitor the progress of the trial. Membership of the IDMC will be proposed by the TMG and approved by the TSC. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU. The IDMC should meet in confidence at regular intervals, firstly to review the safety analysis following the first 5 and 10 patients recruited and at least every 6 months following. A report of the findings and recommendations will be produced following each meeting. This report will be submitted to the TMG and TSC, and if required, the main REC and the MHRA.

The IDMC reserve the right to release any data on outcome or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

17 RESEARCH GOVERNANCE

This Clinical Trial will be conducted in accordance with the ethical principles laid down by the Declaration of Helsinki, 1964 and as amended in 1996 and the principles of Good Clinical Practice.

17.1 Sponsor Responsibilities

The Co-sponsors are The Institute of Cancer Research (ICR) and The Royal Marsden NHS Foundation Trust (RMH). Sponsorship activities and delegated responsibilities are shared between ICR and RMH, in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. Responsibilities of the Co-sponsors are set out in an agreement letter between ICR and RMH.

17.2 Principal Investigator Responsibilities

Responsibilities of each Principal Investigator and participating centre will be detailed in a contract with the Co-sponsors.

Principal Investigator responsibilities include putting and keeping in place arrangements to run the trial at their site according to the trial protocol and applicable guidance notes, The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. The above responsibilities include, but are not limited to, the following:

- Putting and keeping in place arrangements to adhere the principles of GCP
- Keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving and destruction of documentation once the trial has ended as required by regulation 31 of the principal Regulations of the Medicines for Human Use (Clinical Trials) Regulations 2004 implementing the commission directive 2005/28EC
- Ensuring investigational medicinal products (IMPs) are made available to subjects free of charge
- Taking appropriate urgent safety measures and
- Ensuring recording and prompt reporting of SAEs/SARs to ICR-CTSU

ICR is responsible for co-ordinating any required legal agreements and investigator statements.

The delegation of sponsorship responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership

and as such it is necessary to share pertinent information between ICR and RMH/Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

17.3 AstraZeneca Responsibilities

AstraZeneca are responsible on behalf of the co-sponsors for the manufacture, packing, labelling and distributing of study drug and matching placebo to site in accordance with Good Manufacturing Practice and all applicable local legislation. Some of these responsibilities have been delegated by AstraZeneca to Fisher Clinical Services. Responsibilities are defined in an agreement between AstraZeneca and the co-sponsors, and AstraZeneca and Fisher Clinical Services.

18 TRIAL ADMINISTRATION & LOGISTICS

18.1 Protocol Compliance

The TOPARP Trial is being conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the EU Clinical Trials Directive. Before activating the trial, participating centres are required to sign an agreement accepting responsibility for all trial activity which takes place within their centre.

Sites may commence recruitment once centre agreements have been signed by both parties, trial documentation is in place and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

18.2 Data Acquisition

ICR-CTSU is responsible for the data management and statistical analysis of trial data. Electronic (e) Case Report Forms (eCRF) will be used for the collection of trial specific data. The Trial Management Group reserves the right to amend or add to the eCRF as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres in accordance with the guidelines provided by ICR-CTSU.

The clinical data should be recorded in the TOPARP eCRFs in a timely manner.

By participating in the TOPARP trial, the Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure that:

- Sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and eCRFs;
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- All staff at their centre who are involved with the trial will meet the requirements of the EU Directive;
- Original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent;
- All essential documents must be retained for five years after the Trial ends to comply with current legislation.
- Staff will comply with the protocol and Trial Guidance Notes for the TOPARP trial.

Completion of eCRFs will be monitored by ICR-CTSU and any missing forms will be reported to the originating site.

18.3 Central Data Monitoring

Once data has been entered by the site personnel on the eCRF, the ICR-CTSU will review and check the data for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be issued to the centre for resolution.

Data will be further reviewed for data anomalies / missing data, by central statistical monitoring. Any systematic inconsistencies identified may trigger monitoring visits to centres.

18.4 On-Site Monitoring

Site monitoring will be conducted at participating centres at least once during the course of the trial. Additional on-site monitoring may be triggered by routine central statistical monitoring or identification of a new risk to the trial.

If a monitoring visit is required, ICR-CTSU will contact the centre to discuss dates of proposed visit. Once a date has been confirmed, the centre should ensure that the relevant patient notes are available for monitoring.

If any problems are detected in the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator to resolve issues and, if necessary, to determine the centre's future participation in the study.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the site agreement and trial protocol to ensure the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996.

18.5 End of trial

The end of trial for MHRA and MREC purposes is the date of last data capture

18.6 Archiving

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. They should be retained for a sufficient period (at least 5 years after the date of last date of data capture) for possible inspection by the regulatory authorities. Documents should be securely stored and access restricted to authorised personnel.

19 PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

The trial will have received ethical, regulatory and institution specific approvals prior to recruitment of any patients into the study. Before entering patients, the Principal Investigator at each site is responsible for gaining Site Specific Assessment and Research and Development approval of this protocol.

Patients should be asked to sign the trial consent forms after receiving both verbal and written information about the trial. All consent forms must be countersigned by the Principal Investigator or a designated individual. A record listing the designated individuals and the circumstances under which they may countersign consent forms must be clearly documented at the research site as part of the Delegation of Responsibilities Log. This log, together with original copies of all signed patient consent forms, must be available for inspection.

The TOPARP patient information sheets should be provided in addition to any standard patient information sheets that are provided by the centre and used in routine practice.

19.1 Patient Confidentiality

Patients will be asked to consent to their full name being collected at registration in addition to their date of birth, hospital number, postcode and NHS number (CHI in Scotland) to allow tracing through national records to assist with long term follow up and to allow linkage with routinely collected NHS data. The personal data recorded on all documents will be regarded as confidential, and any information which would allow individual patients to be identified will not be released into the public domain.

Each investigator should keep a separate log of all patients' Trial IDs, names, addresses and hospital numbers. The investigator must maintain trial documents, which are to be held at the participating centres (e.g. patients' written consent forms), in strict confidence. The investigator must ensure the patients' confidentiality is maintained.

ICR-CTSU will maintain the confidentiality of all patients and will not reproduce or disclose any information by which patients could be identified. Representatives of ICR-CTSU and the regulatory authorities will be required to have access to patients notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries it is also necessary to have access to the complete study records provided that patient confidentiality is protected.

19.2 Data Protection

ICR-CTSU will comply with all applicable data protection laws. Any requests from patients for access to data about them held at ICR-CTSU should be directed to the Trial Manager in

the first instance who will refer the request to the Data Protection Officer at The Institute of Cancer Research.

19.3 Liability

The Co-Sponsors have taken out an insurance policy to cover their study responsibilities, and certification of this will be provided to the regulatory authorities as required. ICR-CTSU will need to be satisfied that all participating sites have appropriate indemnity arrangements in place.

20 FINANCIAL MATTERS

The trial is investigator designed and led and has been approved by Clinical Trials Advisory & Awards Committee (CTAAC) of Cancer Research UK, and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

ICR has received funding from Cancer Research UK and AstraZeneca (via the AstraZeneca/NCRN collaboration) for the central coordination of the trial. AstraZeneca are also providing olaparib for the purposes of this trial free of charge.

In the UK, the trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research (NIHR) portfolio by virtue of its approval by CTAAC. Therefore, National Cancer Research Network (NCRN) resources should be made available for the TOPARP trial to cover UK specific research costs.

21 PUBLICATION POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group led by the chief investigator, appointed from amongst the Trial Management Group, and participating clinicians. All participating centres and clinicians will be acknowledged in this publication together with the dedicated staff from the ICR-CTSU. All presentations and publications relating to the trial must be authorised by the Trial Management Group, on whose behalf publications should usually be made. Authorship of any secondary publications e.g. relating to the various biological studies will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to the TOPARP trial without prior permission from the Trial Management Group.

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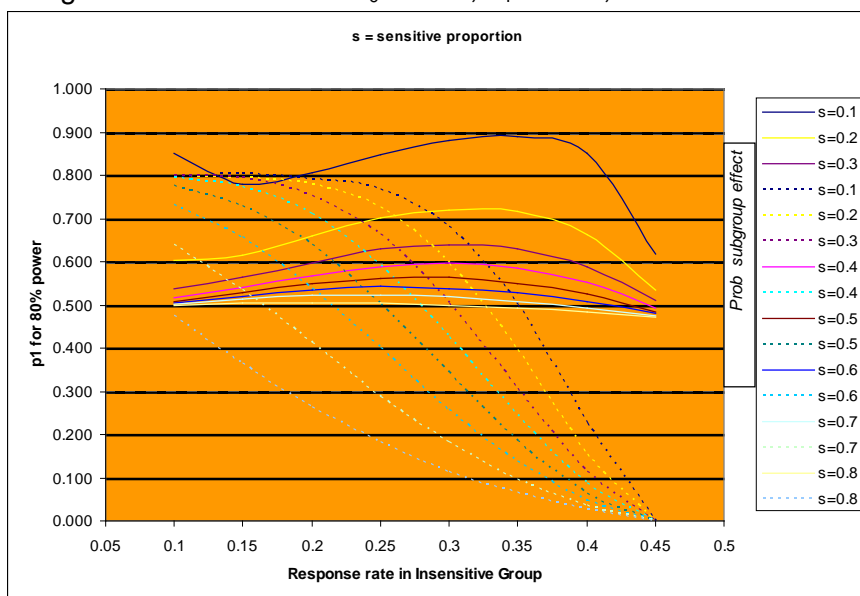
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23 APPENDICES

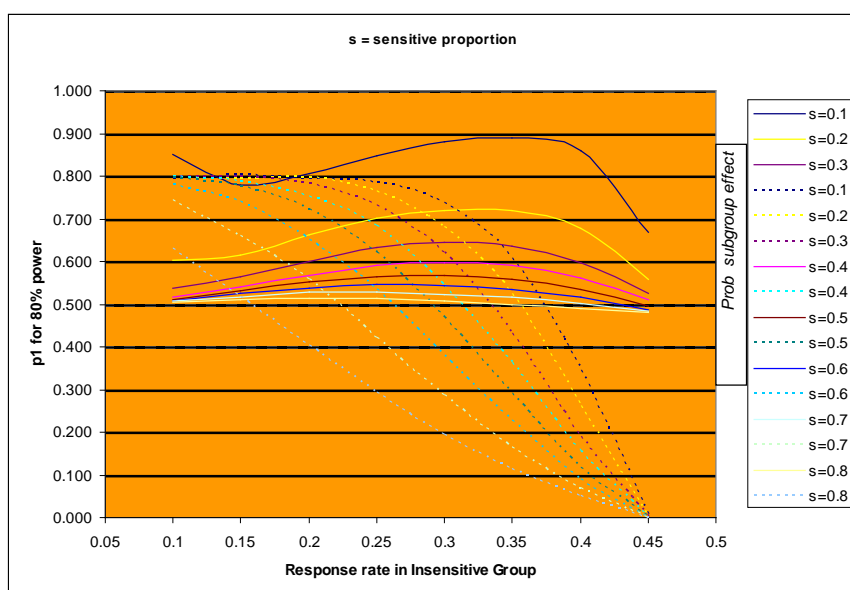
23.1 Appendix A: Detectable Effects

It is possible to calculate detectable effects in the sensitive group (80% power, y-axis) based on the proportion of sensitive patients (individual lines) and the response rate (x-axis) in the insensitive subgroup. Also shown is the probability a subgroup effect is detected (dashed lines), with 80% power this probability cannot exceed 80%. The fall in the probability of detecting a subgroup effect with increasing response rate in insensitive patients is therefore balanced by an increase in the probability of detecting an overall effect. Thus, in the extreme, if the response rate in insensitive patients is 45% and the response rate in sensitive patients is about 50% a conclusion of overall efficacy will be reached with 80% power, for subgroups of size 30% or more.

Using cut offs for Part A of $a_0=15/30$, $a_1=23/45$, as intended.



Using cut offs for Part A of $a_0=18/30$, $a_1=27/45$ the probability of detecting a subgroup effect if the sensitive group is large ($>50\%$) can be improved.



23.2 Appendix B: Sample Size Calculations

TOPARP sample size calculations, **Part A** : alpha 2.2%, Power 90%

Ho : Null Hypothesis Response rate (p0) is 5%

Probability reject		0.97818	<i>alpha</i> 2.2%												
Reject first stage		0.81218	(Probability of early termination, sum of values in light blue)												
Reject second stage		0.166	(sum of values in dark blue)												
N	po	sum 0.97818													
First	0.05														
	0	N second stage													
	1	0	1	2	3	4	5	6	7	8	15			
	2	0.46329	0.3657562	0.13475	0.03073	0.00485	0.00056	4.9E-05	3.3E-06	1.8E-07	3.1E-20			
	3	0.12705	0.059	0.046	0.017	0.004	0.001	0	0	0	0			
	4	0.045136	0.021	0.017	0.006	0.001	0	0	0	0	0			
	5	0.012353	0.006	0.005	0.002	0	0	0	0	0	0			
	6	0.002709	0.001	0.001	0	0	0	0	0	0	0			
	7	0.000489	0	0	0	0	0	0	0	0	0			
	8	7.4E-05	0	0	0	0	0	0	0	0	0			
	9	9.52E-06	0	0	0	0	0	0	0	0	0			
	10	1.05E-06	0	0	0	0	0	0	0	0	0			
	11	1.01E-07	0	0	0	0	0	0	0	0	0			
	12	8.39E-09	0	0	0	0	0	0	0	0	0			
	13	6.11E-10	0	0	0	0	0	0	0	0	0			
	14	3.91E-11	0	0	0	0	0	0	0	0	0			
	15	2.19E-12												
	16	1.08E-13												
	17	4.69E-15												
	18	1.78E-16												
														
	26	3.33E-30													
	27	2.59E-32													
	28	1.46E-34													
	29	5.31E-37													
	30	9.31E-40													

Stage I 2.31E-12
probability of incorrect stopping

H1 : Null Hypothesis Response rate (p1) is 20%

Probability reject		0.10318	<i>Power</i> 89.7%												
Reject first stage		0.04418	(Probability of early termination, sum of values in light blue)												
Reject second stage		0.059	(sum of values in dark blue)												
N	po														
First	0.2														
	0	N second stage													
	1	0	1	2	3	4	5	6	7	8	15			
	2	0.03518	0.1319414	0.2309	0.25014	0.1876	0.10318	0.04299	0.01382	0.00345	3.3E-11			
	3	0.078532	0.003	0.01	0.018	0.02	0.015	0.008	0.003	0.001	0			
	4	0.132522	0.005	0.017	0.031	0.033	0.025	0.014	0.006	0.002	0			
	5	0.172279	0.006	0.023	0.04	0.043	0.032	0.018	0.007	0.002	0.001	0		
	6	0.179457	0.006	0.024	0.041	0.045	0.034	0.019	0.008	0.002	0.001	0		
	7	0.153821	0.005	0.02	0.036	0.038	0.029	0.016	0.007	0.002	0.001	0		
	8	0.110559	0.004	0.015	0.026	0.028	0.021	0.011	0.005	0.002	0			
	9	0.067564	0.002	0.009	0.016	0.017	0.013	0.007	0.003	0.001	0			
	10	0.035471	0.001	0.005	0.008	0.009	0.007	0.004	0.002	0	0			
	11	0.016123	0.001	0.002	0.004	0.004	0.003	0.002	0.001	0	0			
	12	0.006382	0	0.001	0.001	0.002	0.001	0.001	0	0	0			
	13	0.002209	0	0	0.001	0.001	0	0	0	0	0			
	14	0.000671	0	0	0	0	0	0	0	0	0			
	15	0.000179												
	16	4.19E-05												
	17	8.63E-06												
	18	1.56E-06												
														
	26	7.53E-15													
	27	2.79E-16													
	28	7.47E-18													
	29	1.29E-19													
	30	1.07E-21													

Stage I 0.000231
probability of incorrect stopping

TOPARP sample size calculations, **Part A**, rule to be applied if no subgroup is found:

Ho : Null Hypothesis Response rate (p0) is 30%

<u>N</u>	<u>p0</u> 0.3	Reject first stage	0.94505 (sum of values in light blue)	alpha	5.5%
0	1.07E-07	16	0.0896266	32	1.3E-08
1	2.06E-06	17	0.0655253	33	2.2E-09
2	1.95E-05	18	0.0436835	34	3.3E-10
3	0.00012	19	0.0266043	35	4.5E-11
4	0.000538	20	0.0148224	36	5.4E-12
5	0.00189	21	0.0075624	37	5.6E-13
6	0.005401	22	0.0035357	38	5E-14
7	0.012895	23	0.0015153	39	3.9E-15
8	0.026251	24	0.0005953	40	2.5E-16
9	0.046252	25	0.0002143	41	1.3E-17
10	0.071361	26	7.065E-05	42	5.3E-19
11	0.09731	27	2.131E-05	43	1.6E-20
12	0.118162	28	5.87E-06	44	3.1E-22
13	0.12855	29	1.475E-06	45	3E-24
14	0.125927	30	3.371E-07		
15	0.111535	31	6.991E-08		

Ha : Alternate Hypothesis Response rate (p1) is 50%

<u>N</u>	<u>p1</u> 0.5	Reject first stage	0.11635	Power	88.4%
0	2.84E-14	16	0.0183782	32	0.00207
1	1.28E-12	17	0.0313511	33	0.00082
2	2.81E-11	18	0.0487684	34	0.00029
3	4.03E-10	19	0.0693024	35	9.1E-05
4	4.23E-09	20	0.0900931	36	2.5E-05
5	3.47E-08	21	0.1072537	37	6.1E-06
6	2.31E-07	22	0.1170041	38	1.3E-06
7	1.29E-06	23	0.1170041	39	2.3E-07
8	6.13E-06	24	0.1072537	40	3.5E-08
9	2.52E-05	25	0.0900931	41	4.2E-09
10	9.07E-05	26	0.0693024	42	4E-10
11	0.000288	27	0.0487684	43	2.8E-11
12	0.000817	28	0.0313511	44	1.3E-12
13	0.002075	29	0.0183782		
14	0.004743	30	0.0098017		
15	0.009802	31	0.0047428		

TOPARP sample size calculations, **Part B** :

Ho : Null Hypothesis Response rate (p0) is 30%

N	p0	Reject first stage	0.95628 (sum of values in light blue)	alpha	5%
	0.3				
0	1.53E-07	16	0.0825133	32	5.4E-09
1	2.88E-06	17	0.0582447	33	8.4E-10
2	2.66E-05	18	0.037443	34	1.2E-10
3	0.000159	19	0.0219591	35	1.4E-11
4	0.0007	20	0.0117638	36	1.5E-12
5	0.0024	21	0.0057619	37	1.4E-13
6	0.006687	22	0.0025816	38	1.1E-14
7	0.015556	23	0.0010583	39	7.4E-16
8	0.030835	24	0.0003969	40	4E-17
9	0.05286	25	0.0001361	41	1.7E-18
10	0.07929	26	4.261E-05	42	5.1E-20
11	0.105033	27	1.218E-05	43	1E-21
12	0.123789	28	3.168E-06	44	9.8E-24
13	0.130591	29	7.491E-07		
14	0.123928	30	1.605E-07		
15	0.106224	31	3.107E-08		

Ha : Alternate Hypothesis Response rate (p1) is 50%

N	p1	Reject first stage	0.14561	Power	85%
	0.5				
0	5.68E-14	16	0.0236875	32	0.0012
1	2.5E-12	17	0.0390147	33	0.00044
2	5.38E-11	18	0.058522	34	0.00014
3	7.53E-10	19	0.0800828	35	4E-05
4	7.72E-09	20	0.1001035	36	1E-05
5	6.17E-08	21	0.114404	37	2.2E-06
6	4.01E-07	22	0.1196042	38	4E-07
7	2.18E-06	23	0.114404	39	6.2E-08
8	1.01E-05	24	0.1001035	40	7.7E-09
9	4.03E-05	25	0.0800828	41	7.5E-10
10	0.000141	26	0.058522	42	5.4E-11
11	0.000436	27	0.0390147	43	2.5E-12
12	0.001199	28	0.0236875	44	5.7E-14
13	0.002951	29	0.013069		
14	0.006534	30	0.0065345		
15	0.013069	31	0.0029511		

23.3 Appendix C: Evidence of PD to Determine Trial Entry Eligibility

Patients being considered for trial entry should have evidence of disease progression by either PSA, modified RECIST or bone scan to be eligible.

PSA: PSA evidence of disease progression based on the prostate cancer working group (PCWG) 2 criteria consist of a minimum PSA level 2.0 ng/ml that has risen on at least 2 successive occasions, at least 1 weeks apart. The reference value # 1 is the last value before the rise in PSA was observed. If the confirmatory PSA value (Figure 5, # 3A) is greater than the screening value then progression by PSA is met and the patient is eligible for trial enrolment on the basis of PSA alone. If the confirmatory PSA (Figure 5, #3B) value is less than the screening PSA (Figure 5, #2) value, then an additional test for rising PSA (#4) will be required to document progression before the patient can be enrolled.

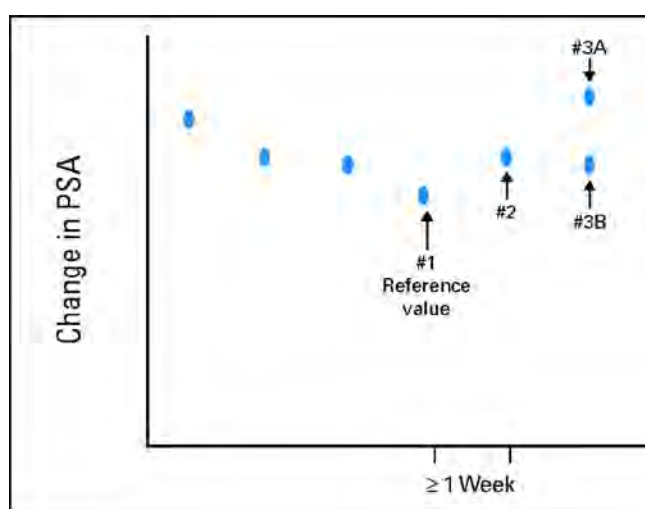


Figure 5: Eligibility Based on PSA

Target lesion/measurable disease: Patients are not required to have evidence of disease progression by measurable disease if they meet the criteria for disease progression on the basis of PSA or bone scan. Evidence of nodal or visceral disease RECIST progression however is sufficient for trial entry independent of PSA readings. Because lymph nodes may be enlarged due to benign pathology, only lymph nodes that are ≥ 2 cm should be used for disease evaluation.

Bone scan: Evidence of disease progression based on bone scan appearance is sufficient for trial entry independent of PSA readings. If the appearance of the bone scan is the only indicator of progression then there must be ≥ 2 new bone lesions compared with the prior bone scans. If there is ambiguity about the appearance of the bony lesions such as traumatic in nature or secondary to a flare reaction then it is recommended that an alternative imaging modality such as MRI or fine-cut CT be used to evaluate these lesions further.

23.4 Appendix D: Outcome Measures of Response / Progression Post Study Treatment

Procedures for Assessing PSA Response / Progression Post Study Treatment

PSA measurements will be done every 12 weeks on day1 of cycle 4,7,10 and every 3rd cycle thereafter. Increases and decreases will be tracked in order to assess disease response. The PSA readings on its own will not be used to define progression in this protocol. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG 2:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA from cycle1day1 (baseline) PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. The first PSA reading will be obtained at week 12.

Duration of PSA Response:

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the Cycle 1 Day 1 (baseline) value that has been confirmed by a second value until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be assessed at the last PSA measurement.

Time to PSA Progression:

For patients who have achieved a $\geq 50\%$ decrease from the Cycle 1 Day 1 (baseline), the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 4 or more weeks later. For patients without a PSA decrease of this magnitude or without a decrease, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented, which is confirmed by a second consecutive value 4 or more weeks later.

Procedures for Assessing Radiological Responses / Progression Post Study Treatment

Categorisation of response in this study will be based on modified RECIST 1.1 for soft tissue disease and appearance of bone scan for bone metastasis.

Bone metastasis evaluation:

The first bone scan should not be performed before 12 weeks post commencement of treatment unless clinically indicated as there may be evidence of a flare response early on which may confuse the response evaluation. A patient will be considered to have progressed on bone scan if the following criteria are met:

- If the first bone scan with 2 new lesions is observed ≤ 13 weeks from the point of Cycle 1 Day 1 and is confirmed by a follow up scan ≥ 6 weeks later showing 2 additional new lesions (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan).
- The first bone scan with ≥ 2 new lesions compared with baseline is observed > 13 weeks from Cycle 1 Day 1 and the new lesions are verified on the next bone scan ≥ 6 weeks later (i.e. a total of ≥ 2 new lesions compared with baseline). If the second scan confirms progression the data of the progression is the date of the first bone scan rather than the second confirmatory scan.

Measurable Disease Evaluation:

Changes in nodal and visceral disease should be recorded using the modified RECIST criteria defined in Appendix E.

Table 8: Radiological Criteria for Ascribing Disease Progression

Evidence of Progression	Confirmation	Action
Bone Disease Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment ≤ 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show an additional 2 new lesions compared to the first post treatment scan (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment > 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should confirm the presence of the 2 new lesions compared the baseline scan. (i.e. a total of ≥ 2 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Soft Tissue Disease as defined by RECIST on CT/MRI	Progression at any scheduled reassessment ≥ 12 weeks does not need to be confirmed.	Investigators are highly encouraged to maintain the patient's treatment with study medication unless radiological progression is observed.

Progression Free Survival (PFS)

In this protocol death, radiographic and unequivocal clinical progression comprise the PFS events. PFS is defined from the time of study entry to confirmed disease progression based on either:

- Radiological progression as documented on bone scans and / or measurable disease on CT scans

OR

- Unequivocal clinical progression

OR

- Death

The analysis of PFS is based on the time of the first progression observed. Where possible all disease assessment (Bone scan, CT, PSA) should be collected at the same time points.

23.5 Appendix E: Modified RECIST

The primary efficacy objective to this trial is based on tumour assessment. For the purpose of this study, definitions of soft tissue tumour assessments will be based on a Modified Response Evaluation Criteria in Solid Tumours 1.1 (RECIST1.1). Pertinent points are summarised below.

Evaluation of measurable and non-measurable lesions

1. **Measurable lesions** – lesions that can be accurately measured in at least one dimension with the longest diameter \geq 20 mm using conventional techniques or \geq 10 mm, with a spiral CT scan.
2. **Non-measurable lesions** – all other lesions, including small lesions (longest diameter \leq 10 mm, with a spiral CT scan), i.e., blastic bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
3. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, should not be included in assessment of response, but should be assessed for progression.
4. For this study, bone lesions are not considered “non-measurable” lesions for RECIST. Bone lesions will be assessed by bone scan only.
5. All measurements should be taken and recorded in metric notation, using a ruler or calipers. Preferably, all screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.
6. The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up.
7. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion is recommended.

Methods of measurement:

1. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.

2. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung, however CT scans are preferable.
3. Ultrasound (US), endoscopy and laparoscopy should not be used to measure tumour lesions. It is however a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound may also be used to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
4. Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions).

Baseline documentation of target and non-target lesions

1. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline and at the time points specified in the protocol.
2. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements.
3. A sum of the longest diameters (LD) for all target lesions will be calculated and reported as the baseline sum of LD. The baseline sum LD will be used as reference by which to characterise the objective tumour response.
4. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions will also be monitored throughout the study, and an overall assessment of response will be made. Details of any new lesions will also be recorded. It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Table 9: Response Criteria

Response criteria	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD)	At least 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	Whether sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Table 10: Responses in patients with both target and non-target disease

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/nonPD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD= progressive disease, NE= inevaluable

Table 11: Responses in patients with only non-target disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/nonPD	No	Non-CR/nonPD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD= progressive disease, NE= inevaluable

Reproduced from: <http://www.recist.com/recist-comparative/01.html> and Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 12 weeks) that is defined in the study protocol.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

23.6 Appendix F: ECOG Performance Status

Table 12: ECOG Performance Status


ECOG Performance Status	Function
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

23.7 Appendix G: National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.02)

V4.02 (CTCAE): publish date August 9, 2010:
ctep.cancer.gov/reporting/ctc.html

23.8 Appendix H: World Medical Association Declaration of Helsinki <http://www.wma.net/e/policy/b3.html>

23.9 Appendix I: Brief Pain Inventory (Short Form)

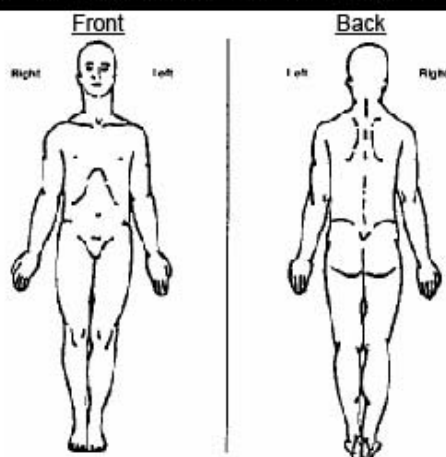
 1903	Date: <input type="text"/> / <input type="text"/> / <input type="text"/> (month) (day) (year)	Study Name: _____ Protocol #: _____ PI: _____ Revision: 07/01/05
PLEASE USE BLACK INK PEN		
Subject's Initials: _____ Study Subject #: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst in the last 24 hours.**

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least in the last 24 hours.**

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the **average.**

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have **right now.**

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

23.10 Appendix J: Total blood volumes drawn at each time point

Study time points	Months on study	Total volume of safety and research bloods per month
Screening	-1	92.5mls
Cycle 1 Day 1	1	156.5 mls
Cycle 1 Day 8		
Cycle 1 Day 15		
Cycle 2 Day 1	2	74mls
Cycle 3 Day 1	3	76.5mls
Cycle 4 Day 1	4	38mls
Cycle 5 Day 1	5	44.5mls
Cycle 6 Day 1	6	24mls
Cycle 7 Day 1	7	38mls
Cycle 8 Day 1	8	12mls
Cycle 9 Day 1	9	12mls
Cycle 10 Day 1	10	38mls
Cycle 11 Day 1	11	12mls
Cycle 12 Day 1	12	12mls
End of study		92.5mls

TOPARP

Phase II Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer

Chief Investigator	Prof. Johann de Bono
Co-Sponsors:	The Royal Marsden Hospital NHS Foundation Trust / The Institute of Cancer Research
Approval:	Cancer Research UK Clinical Trials Awards & Advisory Committee (CTAAC) and Biomarkers Imaging Development and Discovery Committee (BIDD)
Funders:	Cancer Research UK AstraZeneca
Coordinating Trials Unit:	Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU)

PROTOCOL Version 4.0 15th April 2014

EudraCT Number: 2011-000601-49	CTA Number: 22138/0016/001-0001
ICR-CTSU Protocol Number: ICR-CTSU/2011/10030	ICR/RMH CCR Number: 3592
Main REC Reference Number: 11/LO/2019	ISRCTN: 15124653
CR UK Reference Number: CRUK/C12540/A12354	

The TOPARP trial is part of the National Institute for
Health Research Clinical Research Network Trial Portfolio



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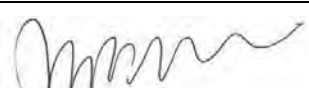
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This protocol describes the TOPARP trial and provides information about procedures for entering patients. The protocol should not be used as a guide for the treatment of other patients. Every care has been taken in the preparation of this protocol, however corrections or amendments may be necessary. These will be circulated to investigators in the trial. Centres entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version. Protocol amendments will be circulated to participating centres as they occur.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended. It will be conducted in compliance with the protocol, the Data Protection Act (Z6364106) and other regulatory requirements as appropriate.

Glossary of Abbreviations and Definitions of Terms

AD	Androgen deprivation
ADP	Adenosine diphosphate
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase (SGPT)
APTT	Activated partial thromboplastin time
AST	Aspartate Transaminase (SGOT)
AR	Androgen receptor
AZ	AstraZeneca
BID	Twice daily
BER	Base excision repair
BP	Blood Pressure
BUN	Blood urea nitrogen
°C	Degrees Celsius
FBC	Full Blood Count
cm	Centimetre
CR	Complete Response
CrCl	Creatinine clearance
CRF	Case Report Form
eCRF	Electronic Case Report Form
CRPC	Castration Resistant Prostate Cancer
CT	Computerised Tomography
CTC	Circulating Tumour Cell
CTCAE	Common Terminology Criteria for Adverse Events
D	Day (as in treatment day)
dL	Decilitres
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DRE	Digital rectal exam
DSB	Double Strand Breaks
DW-MRI	Diffusion-weighted MRI
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
FDA	Food and Drug Administration
FISH	Fluorescent in-situ hybridisation
FBC	Full Blood Count
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyltransferase
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
Ha	Alternative Hypothesis
H2AX	Histone H2AX
Ho	Null hypothesis
HR	Homologous Recombination
IB	Investigator Brochure
IC50	Dose for 50% inhibition
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IF	Immunofluorescence
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRB	Institutional Review Board
ITT	Intention To Treat
kg	Kilogram
LD	Longest Diameter
LDH	Lactic Dehydrogenase
LHRH	Luteinizing Hormone Releasing Hormone
mg	Milligram
MRI	Magnetic Resonance Imaging
miRNAs	MicroRNAs
NAD	Nicotine adenine dinucleotide
NCI	National Cancer Institute
NCICTC	National Cancer Institute Common Terminology Criteria
nM	Nanomolar
NRS	Numeric Rating Scale
ORR	Overall Response Rate
PARP	Poly (ADP-ribose) polymerase
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD	Pharmacodynamic
PFS	Progression Free Survival
PICF	Patient Informed Consent Form
PIN	Prostatic Intraepithelial Neoplasm
PK	Pharmacokinetic
PO	Per Oral (by mouth)
PR	Partial Response
PSA	Prostatic Specific Antigen
PCWG2	Prostate Cancer Working Group 2
PT	Preferred Term
PTEN	Phosphatase and Tensin Homologue
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SD	Stable disease
SUSAR	Serious unexpected suspected adverse (drug) reaction
SBP	Systolic blood pressure
SSB	Single Strand Break
SOC	System Organ Class
µM	Micromolar
ULN	Upper Limit of Normal
UA	Urinalysis
WBC	White Blood Cells

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1 TRIAL SUMMARY

PROTOCOL TITLE	Phase II Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer (TOPARP).
TARGET DISEASE	Castration resistant prostate cancer (CRPC)
STUDY OBJECTIVES	<ul style="list-style-type: none"> To evaluate the anti-tumour activity of olaparib in metastatic castration resistant prostate cancer To identify molecular signatures of tumour cells in responding and non-responding patients To clinically qualify putative predictive biomarkers of PARP inhibitor sensitivity
STUDY DESIGN	Open-label, single arm, two part adaptive design phase II trial.
TRIAL POPULATION	Patients with an advanced CRPC who have failed androgen deprivation and taxane-based treatment.
TREATMENT REGIMEN	Patients will receive single agent olaparib 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.
RECRUITMENT TARGET	Part A: between 30-45 patients Part B: 44 patients
PRIMARY ENDPOINT	Response will be defined on the basis of the following outcomes, if any of these occur patients will be considered to have responded: <ul style="list-style-type: none"> Objective response by modified RECIST PSA decline of $\geq 50\%$ according to the Prostate Cancer Working Group 2 (PCWG2) Conversion of circulating tumour cell count (CTC) from ≥ 5 cells/7.5 ml blood at baseline to < 5 cells/7.5 ml confirmed by a second consecutive value obtained four or more weeks later
SECONDARY ENDPOINTS	<ul style="list-style-type: none"> Radiological progression free survival Time to radiological progression Progression free survival Overall survival Time to PSA progression Proportion of patients with conversion of CTC count from $\geq 5/7.5$ ml blood at baseline to $< 5/7.5$ ml blood nadir Duration of PSA response and objective response (PSA-ORR), if applicable Safety and tolerability of olaparib
EXPLORATORY ENDPOINTS	<ul style="list-style-type: none"> To evaluate the impact of treatment with olaparib on bone metastasis imaging by DW-MRI in selected patients and to correlate these results with PSA, CTC and radiological responses

	<p>by conventional imaging.</p> <ul style="list-style-type: none"> • To determine the proportion of patients achieving pain improvement with olaparib treatment.
<p>TRIAL OUTLINE</p>	<ul style="list-style-type: none"> • There will be screening period of up to 28 days prior to cycle 1 day 1. • Archival tissue is mandated for enrolment into the study. Patients who do not have a prior histological diagnosis or archival tissue available will be required to have a tumour biopsy. PART A of the study will be open to all comers. In PART B the tumour tissue of the patients being considered for enrolment will be analysed first to ensure the presence of the putative predictive biomarkers and only patients with the predictive biomarkers will be enrolled. • Patients will receive single agent 400mg of olaparib, twice daily, continuously on 28-day cycles. • During the study period, no other anticancer or hormonal treatment will be given although a LHRH analogue must be continued, unless the patient is surgically castrate. <p>Efficacy Assessments:</p> <ul style="list-style-type: none"> • Baseline CT scans, bone scan and DW-MRI (optional) will be performed as close as possible to cycle 1 day 1 of treatment. These scans will be repeated after every 3 cycles (12 weeks) or earlier if clinically indicated. • PSA will be assessed at baseline and every 12 weeks by PCWG2 criteria. In the absence of radiological disease progression patients should continue on study. <p>Safety Assessments:</p> <p>Safety parameters will be continuously assessed throughout the study prior to each cycle of treatment. Adverse events (AEs) and serious adverse events (SAEs) including laboratory tests will be graded and summarised according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events version 4.02 (CTCAE v4.02).</p> <p>Based on Phase I and Phase II studies, olaparib is generally well tolerated. Safety concerns are mainly related to the possibility of myelosuppression. Patients who experience a NCI-CTCAE grade 3-4 haematological or non-haematological toxicity that the investigator attributes to olaparib may have an interruption of olaparib treatment for up to 42 days until recovery of all toxicities to no more than NCI-CTCAE grade 1. Those patients on continuous treatment requiring a delay in dosing by >14 days will require a dose reduction to 300mg BID. If the adverse event recurs at the same severity, treatment can be interrupted again and on resolution to ≤ NCI-CTCAE grade 1 toxicity a further dose reduction to 200 mg BID can be made. If the adverse event recurs despite the second dose reduction a final dose</p>

	<p>reduction to 100mg BD is permitted.</p> <p>Olaparib should be withheld in the event of:</p> <ul style="list-style-type: none"> • Grade 4 neutropenia • Grade 2-4 neutropenia with infection • Platelet count lower than $50 \times 10^9/L$ • Non-haematological toxicity grade 3 or greater, except nausea, vomiting or diarrhoea and fatigue associated with suboptimal pre-medication and/or management OR transient and clinically insignificant biochemical blood results. • Aspartate transaminase (AST) or alanine transaminase (ALT) elevations grade 3 or higher for more than 7 days. • Any other toxicity that, in the view of the principal investigator and the medical monitor, represents a clinically significant hazard to the patient until resolution of toxicity to no more than grade 1. <p>Biomarker Assessments:</p> <p>All patients enrolled in the study are required to have archival tumour tissue, fresh tumour biopsies, blood and urine samples collected during the study for the purpose of biomarker analyses including the following:</p> <ul style="list-style-type: none"> • Circulating tumour cells (CTCs): enumeration & molecular characterisation • PTEN and ERG immunohistochemistry (IHC) on primary tumour tissue and fresh paired biopsies • PTEN and ERG immunofluorescence (IF) in CTCs • <i>TMPRSS2-ERG</i> and <i>PTEN</i> fluorescence in situ hybridisation (FISH) studies in primary tumour, paired biopsies and CTCs • γH2AX and RAD51 foci formation in paired tumour biopsies and CTCs • Markers of tumour cell proliferation and cell cycle phase in paired tumour biopsies and CTCs • Circulating plasma tumour DNA • Circulating plasma tumour and whole blood RNA • Urine telopeptides and RNA • Proteomic profile • Metabolomics profile
<p>FOLLOW UP</p>	<p>Patients will be treated until disease progression (radiological progression) or withdrawal from the study for another reason. After discontinuing study treatment patients will be reviewed within 30 +/- 5 days post cessation of treatment for an end of treatment safety assessment and 3 monthly for survival data.</p>

2. INTRODUCTION

2.1 Metastatic Castration Resistant Prostate Cancer

Prostate cancer is the second leading cause of male cancer-related mortality in the United Kingdom (1). While a proportion of patients have indolent disease, curable with local treatment, approximately a third of patients fail local treatment and develop incurable metastatic disease. Androgen deprivation therapy constitutes the mainstay of treatment for advanced prostate cancer. Most patients with advanced disease initially respond to hormonal deprivation therapy; however resistance inevitably develops within 1-3 years and represents a transition to more aggressive and invariably fatal disease. Recent studies have established that androgen signalling continues to play a pivotal role in tumour progression as castration resistance evolves. Androgen receptor (AR) gene amplification, AR overexpression, AR activating mutations and the presence of sufficient intratumoural androgen levels contribute to continued AR signalling despite a systemic castrate state. The recent emergence of the CYP17 inhibitor, abiraterone and other novel antiandrogens such as MDV3100 provide clinical validation that targeting AR signalling remains a useful approach in a significant proportion of CRPC patients (2, 3).

Metastatic prostate cancer is often associated with significant disease-related morbidity. The vast majority of these patients develop bone metastasis with clinical sequelae of bone pain, skeletal fractures, spinal cord compression and haematological compromise. In addition, soft tissue disease is liable to cause urinary obstructions and other problems.

Most CRPC patients have received multiple lines of hormonal manipulation prior to commencing chemotherapy for ongoing disease progression. Docetaxel and more recently cabazitaxel, Sipuleucel-T, alpharadin and abiraterone have demonstrated an overall survival advantage for metastatic CRPC (mCRPC) albeit of only several months (2, 4, 5, 6). Despite these important incremental advances in treatment options, benefits remain modest and the median survival of patients with mCRPC is unsatisfactory at approximately 18 – 36 months. It is clear that there is an urgent need for better treatments that offer durable clinical benefit and further improvement in overall survival for these patients.

Platinum Based Second-line Chemotherapy in Patients with CRPC

Platinum-based chemotherapy in Phase II trials has provided encouraging response rates (PSA and radiological) in the range of 44-60% and a median progression free survival (PFS) of 4-9.5 months in the post-docetaxel CRPC setting (7, 8). Likewise, satraplatin, an orally bioavailable platinum compound, has shown second-line antitumour activity in unselected patients in a Phase III trial, with a 50% PSA decline rate of 33% and a statistically significant PFS advantage in 40% of the patients (9). The lack of survival outcome in this study, despite the anti-tumour activity observed, may in part relate to inter-patient molecular heterogeneity and failure to optimally select the subgroup of tumours most likely to respond to this strategy.

Platinum salts induce interstrand and intrastrand DNA cross-links and consequently increased levels of double-strand (ds) DNA damage. Platinum compounds and PARP inhibitors (PARPi) exert their anti-tumour activity in a similar way by inducing increased ds-DNA breaks which overwhelms the DNA repair machinery in homologous recombination (HR) repair deficient tumours, consequently resulting in tumour cell death. Tumour sensitivity to the Poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib has been shown to correlate with prior platinum sensitivity in HR deficient, *BRCA1/2* mutant cancers (10, 11). It follows therefore that the previously established antitumour activity for satraplatin in prostate cancer supports the widely held premise that there is indeed a subgroup of CRPC that harbour HR DNA repair defects and will benefit from treatment with the PARP inhibitor, olaparib. No platinum is currently approved for the treatment of CRPC; indeed most CRPC remain platinum naïve. Recruitment of patients most likely to benefit based on biomarker driven molecular sub-classification is critically important for the successful development of novel therapies such as olaparib in this disease.

Prostate Cancer Heterogeneity: Clinical and Molecular

Prostate cancer is a highly heterogeneous disease with patients responding differently to treatments and overall having very different clinical outcomes. This is also reflected at a molecular level (12-16). Different molecular variants portend different clinical outcomes possibly secondary to distinct differences in molecular drivers. Despite this, to date, Phase III trials of novel anticancer drugs in this disease have failed to stratify patients on the basis of molecular profile and likely benefit. This inter-patient molecular heterogeneity may, in part, account for the high risk of failure of pivotal Phase III trials of anticancer drugs in this disease. We envision that an improved understanding of the biological and clinical significance of the molecular sub-classification of this disease will positively impact pivotal randomised clinical trials in this disease. The identification of primary tumour prognostic and predictive molecular markers as compared to the currently utilised suboptimal clinicopathological parameters will allow improved patient selection for optimal CRPC treatments thus maximising clinical benefit while avoiding unnecessarily exposure and toxicity in patients unlikely to benefit.

Dissecting Prostate Cancer Heterogeneity by FISH: *PTEN* & *ETS* Gene Rearrangements.

Functional Loss of *PTEN*

Prostate cancer can be molecularly sub-classified using multi-colour fluorescent in situ hybridisation (FISH). Dissecting the molecular profile of prostate cancers in this way has resulted in the characterisation of multiple commonly occurring genetic aberrations implicated in promoting tumour genesis (12, 15, 17, 18). The biological significance of gene rearrangements, deletions and amplifications as well as possible predictive and prognostic relevance are currently being extensively studied. Phosphatase and tensin homologue (*PTEN*), a tumour suppressor gene, negatively modulates the phosphatidylinositol 3-kinase (PI3)/AKT signal transduction pathway which fosters tumour growth, proliferation and survival (19-22). Bi-allelic and mono-allelic deletion of *PTEN* is a common event in prostate cancer and is implicated in tumour pathogenesis and progression (22-25). *PTEN* functional loss is associated with more advanced disease, higher-grade tumours and a worse clinical

outcome (15, 24-27). The frequency of reported *PTEN* inactivation in prostate cancer is variable in the literature, with mono-allelic and bi-allelic loss by FISH in the range of 30-68% (23, 26, 27, 28). Our own analysis has shown a complete loss of *PTEN* expression by immunohistochemistry (IHC) in archival tissue in approximately 50% in patients on the abiraterone phase I-II studies. The variability seen in the literature may be related to tumour stage, tissue processing, and IHC methodology. A recent study of tumour material from 59 patients with CRPC revealed that the *PTEN* gene was deleted in 77% of cases; 25% with homozygous deletions, 18% with homozygous and hemizygous deletions and 34% with hemizygous deletions. Bi-allelic *PTEN* loss was correlated with disease-specific mortality in this study (24).

Evidence for the importance of *PTEN* functional loss in prostate carcinogenesis also comes from transgenic studies. Critically, conditional *PTEN* loss in prostates from transgenic mice leads to the late development of metastatic prostate cancer (29). Prostate restricted overexpression and activation of *AKT*, however, resulted only in prostatic intraepithelial neoplasia (PIN) formation (30). These data suggest that *PTEN* loss may possibly induce prostate carcinogenesis not only through its phosphatase PI3K/*AKT* regulatory role but also possibly through its nuclear, DNA repair, role that has been recently reported (31, 32).

***TMPRSS2* Chromosomal Translocation**

Chromosomal translocation involving the androgen-responsive gene transmembrane protease serine 2 (*TMPRSS2*) with the oncogenic erythroblast transformation specific (*ETS*) transcription factor family of genes (*ETV1*, *ETV4*, *ETV5*) is reported in 50%-70% of prostate cancers (17, 33). *TMPRSS2/ERG* is the predominant type of gene fusion seen and results in overexpression of 3'-*ERG* sequence joined to the 5'-*TMPRSS2* promoter. Less frequently *TMPRSS2* becomes fused to *ETV1* and *ETV4*. *ERG* and other *ETS* family members are transcription factors that are implicated in the control of cell growth and differentiation. *TMPRSS2/ERG* fusion rearrangement has been shown to co-operate with *PTEN* haploinsufficiency to promote carcinogenesis (17, 22, 34) and accounts for continued hormone driven disease (35). Recent evidence implicates topoisomerase IIB-mediated DNA breakage during the induction of transcriptional programs in generating these *TMPRSS2/ERG* fusion rearrangements (36, 37, 38).

We have utilised validated FISH assays to evaluate *PTEN* deletions and the commonest *ETS* gene rearrangements (*ERG* and *ETV1*) on the Trans-Atlantic Prostate Group (TAPG) tissue microarray (TMA) (15). We demonstrated that patients with *PTEN* loss (heterozygous or homozygous: 17% of newly diagnosed cancers) had significantly worse cause-specific and overall survival compared with patients with no *PTEN* loss, supporting the haploinsufficiency proposed for the *PTEN* gene (Figure 1). Three hundred and eight patients with both *ETS* gene (*ERG* and *ETV-1*) rearrangement and *PTEN* loss status available were analysed for survival outcome (Figure 2). The largest group of patients (n=167, 54%) had no *ERG* or *ETV-1*-gene rearrangement and no *PTEN* loss and had the best outcome with 85.5% survival at 11 years. A poor prognosis group was also identified (n=19, 6%) who had *PTEN* loss but no *ERG* or *ETV-1*-gene rearrangement with a cause-specific survival of 13.7% at 11 years and a median survival of 5 years from diagnosis. Patients with an *ETS* gene rearrangement with or without *PTEN* loss had an intermediate prognosis in keeping with the hormonal sensitivity of these cancers, which has recently

been described (15, 27). Overall, therefore, these data indicate that prostate cancer is a molecularly heterogeneous disease, with cancers demonstrating PTEN loss having a poor outcome, and that to accelerate the successful development of targeted therapies in CRPC, identifying the appropriate subgroup of patients most likely to benefit is paramount.

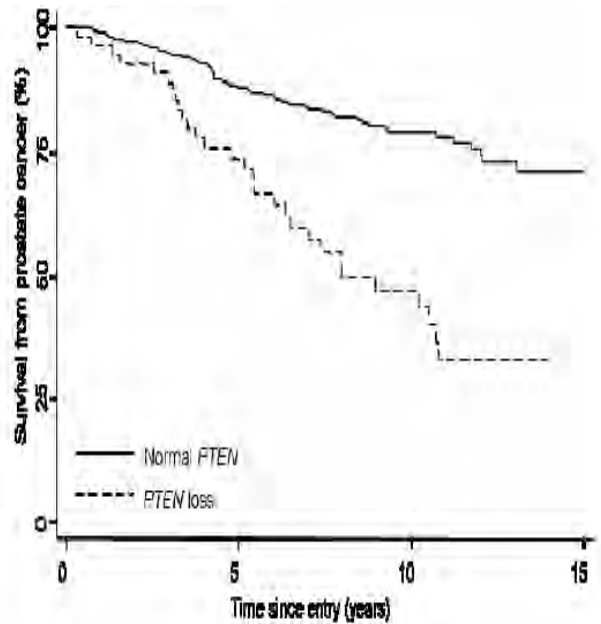


Figure 1: PTEN loss prostate cancers have a worse overall survival

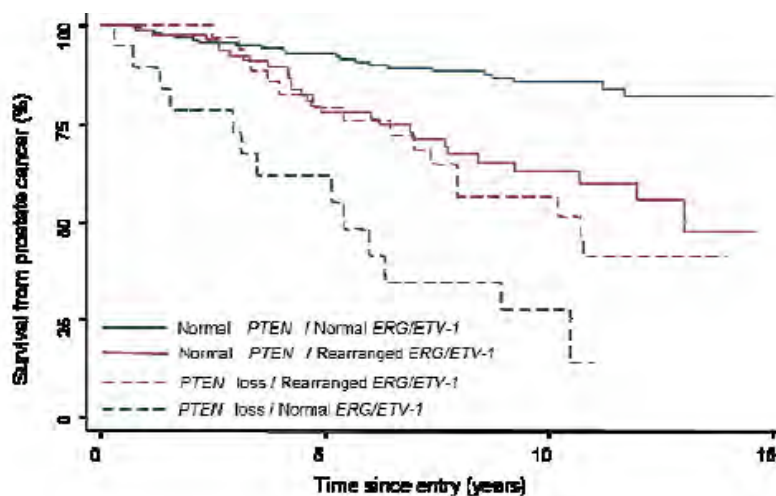


Figure 2: Multi-colour FISH based stratification by studying *ETS* rearrangements and PTEN loss.

PTEN Loss, *ETS* Gene Rearrangements and HR Repair Defects

PTEN is implicated in many functions, both PI3K/AKT dependent and independent. Recent reports suggest in addition to lipid phosphatase function, PTEN localises to the nucleus and that its function includes maintenance of genomic stability (31, 32) by a number of mechanisms including interacting with CENP-C an integral centromeric binding and

stabilising protein, regulating the transcription of RAD51, a critical DNA double strand break (DSB) repair protein (39) and modulating cell cycle progression (40).

PTEN loss results in impaired HR DNA repair with reduced RAD51 expression, increased chromosomal aberrations and genomic instability (31,39). Moreover, in vitro cell-based experiments and in vivo xenograft studies have established that PTEN deficient tumour cells much like *BRCA1/2* deficient tumours are selectively sensitive to platinum compounds and potent PARP inhibitors including olaparib (41-43). Furthermore, restoration of PTEN expression in PTEN deficient tumour cell lines restores PARP inhibitor resistance, confirming PTEN as a determinant of the response to PARP inhibition. This synthetic lethal relationship between PTEN-null tumours and PARP inhibition supports the therapeutic utility of PARP inhibitors in PTEN-deficient tumours. Moreover, *ERG*, the oncogene driven by the commonest prostate cancer genetic driver lesion *TMPRSS2/ERG*, has been shown to directly associate with PARP and requires PARP for its transcriptional regulatory function with PARP inhibition having antitumour activity in *ERG* rearranged tumour models (44,45).

Given these pre-clinical observations and the putative role of PTEN in maintaining chromosomal stability, we predict that tumours with PTEN loss and /or *ETS* gene rearrangements are likely to be hypersensitive to PARP inhibition. We therefore aim to evaluate the antitumour activity of olaparib in patients with sporadic CRPC using an adaptive biomarker driven design to identify and clinically qualify predictive biomarkers of olaparib sensitivity for optimal patient selection.

2.2 PARP and PARP Inhibition

Poly(ADP-ribose) polymerase 1 (PARP-1) is a zinc-finger DNA-binding enzyme that is activated >500 fold upon binding to DNA double or single strand breaks (46). PARP-1 (113 kDa) and PARP-2 (62 kDa) are thus far the only members of the PARP enzyme family known to be involved in DNA damage signalling and repair with a degree of functional redundancy between these proteins. PARP-1 signals the presence of DNA damage and plays a critical regulatory role in DNA damage repair. PARP-1 is involved in a wide range of cellular processes including DNA repair and maintenance of genomic integrity, regulation of protein expression at the transcriptional level, regulation of cellular replication and differentiation, regulation of telomerase activity, and involvement in the cell apoptotic pathway (47).

PARP-1 comprises 3 domains, the N-terminal DNA-binding domain containing 2 zinc fingers, the auto-modification domain and the C-terminal catalytic domain. PARP-1 binds to both single and double-stranded DNA breaks through the zinc-finger domain and catalyses the cleavage of nicotinamide adenine dinucleotide (NAD)⁺ into nicotinamide and ADP-ribose, and subsequently transfers successive units of ADP-ribose onto DNA, histones, PARP-1 and other DNA repair proteins to form branched ADP-ribose polymers. These branched ADP-ribose polymers result in post-translational modification of histones and other nuclear proteins which convert the DNA damage signal into intracellular signals that activate either DNA base-excision-repair (BER) pathways or cell death if the damage is beyond repair. Other transcriptional factors and signalling molecules are also poly-ADP-

ribosylated by PARP-1 to initiate a multitude of other important cellular functions (47,48). Given the critical role that PARP plays in single strand DNA repair it is not surprising that PARPi are able to potentiate the cytotoxic damage incurred with DNA-damaging chemotherapy agents and ionizing radiation (49). PARP inhibitors have also shown significant single agent activity in tumours with HR deficiency (10,11, 50,51).

Synthetic Lethality Between *BRCA1/2*-mediated Homologous Recombination Repair and PARP-1

Abrogating PARP dependent BER, which is responsible for repairing DNA single strand breaks (SSBs) results in the accumulation of SSBs. These SSBs collapse at the replication forks during DNA synthesis giving rise to double strand breaks (DSBs) that are detrimental to the cell. The DNA DSBs are preferentially repaired by high fidelity HR repair that restore genomic integrity under normal circumstances. *BRCA1* and *BRCA2* genes encode proteins that are essential in HR repair. *BRCA1/2* deficient tumour cells lack HR repair capacity and are therefore unable to repair these replication associated DSB DNA damage, which accumulates in the context of suppressed PARP activity, leading to chromosomal instability, cell cycle arrest and apoptosis. The profound selective sensitivity of *BRCA* deficient tumour cells for PARPi compared with unaffected heterozygous mutant normal tissue retaining one functional *BRCA* allele provides a large therapeutic window (47,52,53).

Preclinical models have demonstrated that HR deficient tumour cells with *BRCA1*^{-/-} and *BRCA2*^{-/-} genotype are exquisitely sensitive to PARP inhibition with olaparib (previously referred to as KU-0059436 or AZD2281 in earlier studies), in contrast to heterozygous mutant or wild-type cells (52). Likewise, in the clinic, olaparib is an efficacious therapy with durable antitumour activity and a favourable toxicity profile in HR deficient tumours arising in *BRCA1* and *BRCA2* mutation carriers including several patients with mCRPC (11).

Epigenetic Disruption of *BRCA 1/2* Function and Other Causes of HR Impairment

It has been hypothesised that targeting SSB DNA repair with PARPi will be a useful therapeutic strategy in sporadic tumours that harbour HR repair defects. This may occur due to either epigenetic or genetic silencing of *BRCA1/2* function or disruption of any of the other key proteins that make up the HR repair pathway. Loss of *BRCA 1/2* function may arise spontaneously via somatic mutations and epigenetic mechanisms during tumour formation. These somatic mechanisms of *BRCA1/2* functional loss are increasing implicated in sporadic carcinogenesis (54,55). Epigenetic gene silencing of tumour-suppressor genes is a well-recognised phenomenon with methylation of the *BRCA1* promoter found in 11-14% of sporadic breast cancers and 5-31% of ovarian cancers (56). Epigenetic modification of the Fanconi anaemia/*BRCA* pathway through promoter hypermethylation in lung, oral cancer and cervical cancer cell lines render these cells highly sensitive to DNA cross-linking agents (57,58). Somatic mutations of *BRCA* genes and heterozygous loss also appear to be more common than previously defined (54,58,59). The term “BRCAness” is commonly used to describe the phenotypic likeness of a sporadic tumour with a familial-*BRCA1/2* mutation related cancer (56). Identification of this BRCAness phenotype secondary to epigenetic / genetic silencing of the Fanconi anaemia/*BRCA* pathway may select for clinical benefit from PARPi in these sporadic cancers.

In addition to somatic *BRCA1/2* dysfunction, disruption of any of the other critical proteins that make up the HR repair pathway such as RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHEK1, CHEK2, FANCD2, FANCA or FANCC 2 have been shown in preclinical models to cause HR deficiency and render these tumour cells highly susceptible to synthetic lethality with PARPi (56, 60, 61).

Clinical evidence supporting single agent olaparib antitumour activity in sporadic cancer was recently reported (58,62,63), with durable objective responses observed in 28% of sporadic high grade serous ovarian cancers in one study and a further study reporting a significant improvement in progression free survival (62,63). These responses may be explained in part by the high frequency of somatic mutations of *BRCA1/2* as well as epigenetic silencing of this and other key HR genes in high grade serous ovarian cancer (58). These results have led to the further evaluation of single agent olaparib in other tumour types enriched for HR defects. Identifying the subgroup of sporadic tumours with HR defects through validated predictive biomarker studies is imperative, if we are to successfully develop novel treatments such as PARP inhibitors (PARPi) and personalise medicine.

There has been limited investigation to date of the incidence of somatic aberrations in key HR related genes in advanced prostate cancer. High penetrance germline mutations in several candidate genes involved in DSB repair including *BRCA1*, *BRCA2*, *CHEK2*, *BRIPI/FANCI* and *NBS1* are known to account for a small fraction of prostate cancer cases (64-70). *PTEN* however is one of the commonest tumours suppressor genes that is deregulated in prostate cancer and is implicated in the pathogenesis of this tumour as discussed above. Loss of *PTEN* function may also result in deficient HR DNA repair with reduced RAD51 expression and sensitivity to PARP inhibition (39,41). Likewise, the *ERG/TMPRSS2* gene rearrangement which is observed in 50% of prostate cancers is also implicated in conferring sensitivity to PARPi (44). Overall, these data support the evaluation of PARP inhibitors in the treatment of advanced prostate cancer.

2.3 Rationale for Study

Despite recent advances in CRPC treatment, metastatic prostate cancer remains a common disease with a poor outlook. Improved treatments that offer durable clinical benefit and significant survival impact remain an area of unmet medical need. As with most chemotherapies, a proportion of prostate cancers will not respond due to the underlying tumour biology and inherent resistance mechanisms. Understanding the underlying molecular determinants of response and resistance to different treatments is critical for improvement in CRPC patient outcome through optimally selected treatments.

The previously established antitumour activity of platinum based regimens in advanced prostate cancer suggests that there is a subgroup of CRPC susceptible to DNA damaging agents such as platinum and PARPi.

The PARP inhibitor, olaparib is a novel anticancer agent with strong preclinical and clinical data for significant antitumour activity in HR repair deficient tumours arising in *BRCA1* and *BRCA2* mutation carriers including a number of patients with metastatic CRPC

(10,11,50,51,52,53). Recent clinical evidence supports the utility of this approach in sporadic high-grade ovarian cancers enriched for HR defects (62,63). Moreover, there is a growing body of preclinical evidence that supports extending this approach to a wide range of other sporadic tumours with disruption to other non-redundant components of the HR repair pathway including RAD51 and other essential HR repair proteins (60,61). Identifying these sporadic tumours with HR repair defects through validated predictive biomarkers remains a challenge and focus of ongoing research.

PTEN loss has been implicated to confer HR DNA repair defects with reduced RAD51 expression, increased genomic instability and tumour sensitisation to PARP inhibition (41-43). Homozygous *PTEN* loss by FISH is present in 20-30% of CRPC, with loss of protein expression by IHC being far more common (21). In addition, the *TMPRSS2/ERG* driver rearrangement, which is present in approximately 50-60% of prostate cancers and co-associates with *PTEN* loss has also been reported to confer sensitivity to PARP inhibition (44,45).

The target population for this trial are patients with advanced metastatic CRPC progressing following docetaxel treatment. A proportion of patients may also have received treatment with abiraterone and cabazitaxel. Given the high prevalence of loss of *PTEN* function and *TMPRSS2/ERG* rearrangements in this population and the strong preclinical rationale for this therapeutic strategy, we anticipate that a subgroup of these patients will benefit from olaparib treatment.

Patients may continue olaparib treatment until disease progression or treatment intolerance. Patients may however withdraw from the study at any point if they choose to do so or if the investigator believes it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for reducing the dose of olaparib are provided.

Rationale for Circulating Tumour Cell Based Studies in CRPC

Enumeration of circulating tumour cells (CTC) number using the Cell Search system (Veridex, PA) is a valid biomarker to monitor the effectiveness of therapy of patients with metastatic breast cancer (71-73), colorectal cancer (74) and prostate cancer (75-78). High baseline counts have consistently been associated with more aggressive disease and a worse outcome (76-78). CTC counts are highly prognostic for overall survival, and CTC count falls post-treatment associate with an improved overall survival and response to therapy in CRPC. In a pilot study, univariate analysis demonstrated that CTC counts of $< 5/7.5$ ml blood or $\geq 5/7.5$ ml blood correlated with OS (0.002; HR=7.37); in multivariate analyses CTC counts and PSA doubling time were the only 2 independent predictors of outcome unlike PSA, Gleason score, presence and absence of bony metastasis and age (75). In a similar study that related changes in CTC counts in patients with CRPC during the first 2 cycles of treatment with clinical outcome, we observed that patients with CTC counts that remained below 5 cells/7.5 ml blood during treatment with cytotoxic therapy had the best outcomes, whilst patients whose counts changed from $\geq 5/7.5$ ml blood to ≤ 5 had improved outcomes compared to the patient cohort whose CTC count remained persistently elevated at $\geq 5/7.5$ ml blood throughout treatment. In addition, patients whose CTC counts

increased during treatment from < 5 to $\geq 5/7.5$ ml blood had a similar poor outcome to the group whose count remained persistently elevated at ≥ 5 CTCs throughout treatment suggesting the development of treatment resistance (76). CTC counts were commonly detected in patients with advanced CRPC; CTC counts $>5/7.5$ ml were detected in 19/49 (39%) and 21/28 (75%) of chemotherapy –naïve and post–docetaxel patients respectively treated on the phase I-II Abiraterone studies (35). We now have data from almost a thousand patients participating in the randomised Phase III abiraterone trial (COU-301) that CTC conversion from ≥ 5 to <5 as well as any fall in CTC from 10% to 90% count post-treatment at 1, 2, 3 months after starting abiraterone is a statistically robust surrogate/intermediate endpoint of overall survival, meeting all of Prentice's criteria for surrogacy (78)

In addition, CTCs have been shown to retain many of the genomic characteristics of the primary tumour and thus provide a useful opportunity to study molecular changes in the disease profile longitudinally with ongoing treatment. Multicoloured FISH assays have been successfully applied to determine commonly found genomic alterations such as AR amplification, *PTEN* deletions and *TMPRSS2/ERG* fusion rearrangements in prostate CTCs (35,79,80). We have also developed multiplex immunofluorescence assays to evaluate protein expression in CTCs.

Rationale for Radiographic PFS and 6 months PFS as an Endpoint

Clinical research in prostate cancer has been hindered by the difficulty in objectively defining cancer progression. Composite endpoints that include patient reported, radiographic, and skeletal-related events have suffered from subjectivity. Conventional RECIST alone has limitations in CRPC in defining radiographic progression due to the fact that fewer than 50% of men with CRPC have measurable lesions greater than 2cm in size, and most of these lesions are in lymph nodes which impact survival less than visceral metastases (81). Conventional RECIST also lacks the sensitivity to differentiate true progression of bone metastasis from the flare phenomenon on bone scan or CT scan due to healing of previous bone metastasis (82,83). Although radiographic PFS is not a surrogate for overall survival in patients receiving docetaxel therapy, it outperforms PSA based progression (83).

Attribution of disease progression due to tumour flare phenomenon will be mitigated in this study by applying the new consensus guidelines that requires a confirmatory bone scan at least six weeks after the original scan to define progression. This will reduce the number of false positive determinations of CRPC progression. (Refer to Appendix D)

Progression of metastatic bone disease is of paramount importance to CRPC patients since it is responsible for severe morbidity of skeletal related events such as fracture, pain, and spinal cord compression. Similarly, progression of soft tissue metastasis may be associated with clinically significant morbidity. Prevention or delay in cancer progression should result in clear clinical benefit to the patient. In conclusion, radiologic PFS (rPFS) is an objective measurement that may associate with clinical benefit in the proposed study population.

Pain and Analgesic Assessments

Pain due to bone metastases and nerve root compression is a common experience for patients with advanced prostate cancer. Pain has previously been shown to significantly associate with overall survival in advanced prostate cancer. The McGill Pain Questionnaire (MPQ) (PPI score 0-2 versus 3-5) successfully stratified the survival of first line chemotherapy patients in TAX 327 (84,85).

The BPI-SF, a numeric rating scale (NRS), has been selected as the pain instrument for this study due to the high correlation of numeric rating scales with verbal descriptor scales (e.g. MPQ PPI) (86) and its prior use in other metastatic prostate cancer studies (87,88). The BPI-SF assesses both the intensity of pain and the interference in the patient's function caused by their pain (89). The BPI-SF data can potentially help illustrate the overall benefit of treatment on pain. Analgesic usage will be scored according to the WHO analgesic ladder: 0 for no analgesic, 1 for non-opioid analgesics (including NSAIDs, paracetamol / acetaminophen, antidepressants, and agents intended to treat neuropathic pain), 2 for opioids for moderate pain, and 3 for opioids for severe pain (90).

3. BACKGROUND THERAPEUTIC INFORMATION

Olaparib

Olaparib previously referred to as AZD2281 or KU-0059436 in earlier studies is a potent inhibitor of PARP-1. Olaparib shows significant monotherapy activity in tumour cells with defective components of HR, such as cells with the *BRCA1* *-/-* and *BRCA2* *-/-* genotype both preclinically and clinically (10,11,50,51,52,53,62,63). Selective tumour sensitivity to this PARP inhibitor has also been observed in tumour cells with loss of PTEN function and *ETS* gene rearrangements (41,42,44). This sensitivity in pre-clinical models is expected to translate to clinical benefit.

3.1 Pre-clinical Experience with Olaparib

This pre-clinical and clinical experience with olaparib (AZ2281, KU0059436) is fully described in the Investigator Brochure (IB). Key findings are summarised below.

Pharmacokinetic Data

The olaparib molecule shows cellular activity in the low nM range with a cellular dose for 50% inhibition (IC₅₀) of 2 nM in HeLa cells. Distribution of olaparib is typical for an orally administered foreign compound, in the gastro-intestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. The oral bioavailability of olaparib when dosed at 5mg/kg via a solution formulation was 17% and 19% in male and female rats and 79% *-/+* 12 in male dogs. An oral study of olaparib demonstrated bioavailability of >85% for both 5% and 20% w/w microionised dispersion of the drug substance in Gelucire. Following single oral dosing (5mg/kg), absorption was rapid with an AUC of 10.3 \pm 2.01 in

dogs. The estimated $t_{1/2}$ for olaparib was 3.0, 2.5 and 4.61 \pm 1.66 hours in female rats, male rats and dogs respectively. Multiple oral dosing of olaparib in 28-day rat and dog studies demonstrated that absorption was rapid and exposure increased greater than proportionally with dose across the dose range examined (upto 15mg/kg/ day in dogs and upto 40mg/kg in rats). Plasma protein binding of olaparib varied between 70.4% and 58.8% in rat and dog studies. Metabolism data to date is limited and further investigations are ongoing. To date, several metabolites have been observed in pre-clinical studies. Similar metabolite profiles were observed in the urine and faeces of male and female rats. Excretion is primarily via the faeces and to a lesser extent, the urine. In a study of [14 C]-olaparib in the rat, excretion was 76 \pm 13% in faeces and 20 \pm 11% in urine. For more detailed preclinical data please refer to the IB.

Toxicology and Safety Data

Olaparib has shown comparatively low toxicity in rodent and dog toxicology studies. Oral doses of olaparib were well tolerated for up to 6 months in safety studies and showed no cardiovascular, respiratory, central, peripheral and autonomic nervous system toxicity findings that were a concern. The toxicology studies indicate that the target organ of toxicity is the bone marrow. Specific *ex vivo* work has been conducted exposing human bone marrow cells to olaparib, which has confirmed that olaparib is also active against human bone marrow. The cytotoxic effect becomes evident at a higher concentration than that which fully ablates PARP activity (mean IC₅₀ of 2.7 μ M for myelosuppression [n = 4 human donors] compared with 0.1 μ M for total PARP-1 activity inhibition). These data, along with the 28-day dog and rat studies, show a myelotoxic effect that is mild-to-moderate and is reversible. Platelets appear first affected, followed by white blood cells. Importantly, oncology clinics are used to monitoring for the onset of such effects and are expert in their management.

Olaparib showed no mutagenic potential in the Ames test. Olaparib was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test, and was genotoxic in the rat micronucleus test. Reproductive toxicology data indicate that olaparib can have adverse effects on embryofetal survival and development at dose levels that do not induce maternal toxicity. These findings are not uncommon for many therapeutic agents used in oncology, and so do not present an unacceptable risk when appropriately clinically managed. For further details on these tests or on the fertility studies please refer to the IB.

3.2 Clinical Experience with Olaparib

3.2.1 Pharmacokinetic (PK), Pharmacodynamic (PD) Data

In the Phase I study, patients with solid tumours were given olaparib at a starting dose of 10mg for the first 14 days of a 21-day cycle with a subsequent protocol amendment, changing the dose schedule to continuous daily dosing starting at 100 mg BID for a 28-day cycle. Absorption was rapid and a peak plasma concentration was observed between 1-3 hours post dosing with a terminal elimination half-life of 6.10 hours, supporting twice daily dosing. Drug exposure increased dose proportionally with doses up to 100 mg but increase less than dose proportionally thereafter. The mean volume of distribution and mean plasma

clearance are approximately 40.3 L and 4.55 L/h. On multiple dosing, there was no evidence of any time dependency of the PK and no marked accumulation. Exposure increased proportionally with dose at doses up to 100 mg twice daily but increased in a less than proportional fashion at higher doses. There was no evidence of any marked ethnic difference in PK of olaparib between Japanese and Caucasian patients. Following dosing to cancer patients at doses of 400 mg BID, the population estimated maximum plasma concentration at steady state ($C_{max\ ss}$) ranged from 1.45 $\mu\text{g}/\text{mL}$ to 11.0 $\mu\text{g}/\text{mL}$ (3.34 μM to 25.3 μM , equivalent to unbound concentrations of 0.26 $\mu\text{g}/\text{mL}$ to 1.99 $\mu\text{g}/\text{mL}$ [0.6 μM to 4.58 μM]); the steady state area under the plasma concentration-time curve (AUC) (area under plasma concentration-time curve from zero to 12 h [AUC₀₋₁₂]) ranged from 6.56 $\mu\text{g}\cdot\text{h}/\text{mL}$ to 122 $\mu\text{g}\cdot\text{h}/\text{mL}$.

The distribution of olaparib is typical for an orally administered compound, in the gastrointestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Following administration of a radiolabelled dose of olaparib to cancer patients, olaparib accounted for approximately 70% of the circulating material in the plasma with the remainder accounted for by 3 other components (each accounting for approximately 10% of the material), all of which were also present in the excreta. Drug-related material was eliminated in the urine (35% to 50%) and in the faeces (12% to 60%) with 10% to 20% and 0.6% to 14% of the dosed material recovered in the urine and faeces as unchanged drug, respectively. A further 35 and 19 drug related components were excreted in the urine and faeces, respectively. The metabolites produced were predominantly a consequence of hydroxylation, oxidation or dehydrogenation of the piperazine carboxycyclopropyl, the flourophenyl and the phthalazinone ring system.

Evidence of inhibition of PARP-1 activity has been seen in peripheral blood mononuclear cells (PBMC) and tumour samples from patients dosed with olaparib at all dose levels studied (10 mg to 600 mg) but the data shows wide inter-individual variability in the extent of inhibition achieved and no evidence of any relationship between extent of inhibition and dose administered. Concentration-response curves for inhibition of PARP-1 activity in both PBMC and tumour samples have been generated from a population PK-PD analysis of the data. The population average maximal extent of inhibition in PBMC and tumour samples were 50.6% and 70%, respectively, with maximal inhibition achieved at plasma exposures (steady state AUC) in excess of 1 $\mu\text{g}\cdot\text{h}/\text{mL}$ (exposures which would be expected to be reliably achieved following doses of >40 mg). The potential clinical benefit of continuous dosing is supported by preclinical studies, which show that tumours re-grow after short-term use (e.g. 14 days) and that continuous PARP inhibition with olaparib was able to prevent tumour re-growth. The maximum tolerated dose of olaparib established in the Phase I trials was 400 mg twice daily, continuously (10).

3.2.2 Efficacy Data

The phase I study was enriched with *BRCA1* and *BRCA2* mutation carriers with advanced tumours in the escalation and expansion phase given the strong preclinical rationale of selective tumour killing in *BRCA1/2*-deficient cell lines. In the Phase I study, 41% of 46 evaluable patients with *BRCA*-mutant ovarian cancers achieved objective responses

(complete or partial responses) either by Gynecologic Cancer Intergroup (GCIG) CA125 or RECIST criteria and a further 11% of patient's attained RECIST disease stabilisation (10,11). The encouraging clinical benefit rate of >50% in the subpopulation of *BRCA1/2* mutation cancer patients provides compelling evidence of single agent PARP inhibitor activity in *BRCA*-deficient cancer patients. Durable antitumour responses have also been reported in *BRCA* mutated breast and prostate cancer patients with one prostate patient ongoing treatment for more than 2 years (10, 11, 50, 51).

Two parallel open-labelled multicentre phase II studies of olaparib in *BRCA1/2* mutation carriers with advanced breast and ovarian cancer have confirmed the significant therapeutic efficacy of PARPi in this population (50, 51). 54 breast cancer patients and 56 ovarian cancer patients with advanced heavily pre-treated disease were recruited to 2 non-randomised sequential dose cohorts of 400mg and 100mg BID of olaparib. Following efficacy assessment of the 2 dose levels; patients on the 100mg BID cohort in both studies were allowed to increase the dose of olaparib to 400mg BID given the improved antitumour activity seen at the higher dose level. The breast cancer study reported an objective response rate (ORR) of 41 % (11/27) with 1 complete response (CR) and 10 partial response (PR)s and a median progression free survival (PFS) of 5.7 months (m) (range 4.6-7.4m) at 400mg BID in contrast to an ORR of 22% (6/27) with 6 PRs and a median PFS of 3.8m (range 1.9-5.5m) at the lower dose level (27). In the ovarian study, patients on the 400mg BID and 100mg BID dose levels showed an ORR of 33% (11/33) versus 13% (3/24) by RECIST criteria, a response by either RECIST or by GCIG criteria of 61% (20/33) versus 17% (4/24) and a median duration of response of 290 days (range: 126-513 days) versus 269 days (range:169-288 days) respectively (50). Both dose levels demonstrated clinical activity, however the 400mg BID was more efficacious with improved outcomes establishing substantial antitumour activity for olaparib at a dose of 400mg BID in heavily pre-treated, *BRCA* mutant advanced breast and ovarian cancer patients (50,51). A further phase II study of olaparib at 400mg BID in patients with sporadic high grade ovarian cancer showed an objective response rate of 28%. This study provided the first clinical evidence for the antitumour activity of olaparib in sporadic serous ovarian cancers (62). Most recently, patients with sporadic platinum sensitive serous ovarian cancer who previously achieved either a partial or complete response from platinum therapy demonstrated a doubling of the progression free survival (PFS) from 4.8months to 8.4months with 400mg BID olaparib maintenance treatment compared to placebo. The hazard ratio (HR) was 0.35 (95% CI: 0.25, 0.49; p<0.00001) (63).

3.3 Summary of Clinical Toxicity Data

The clinical experience with olaparib is fully described in the IB and largely has been conducted with the Gelucire® 44/14 (capsule) formulation.

As of 20 May 2011, 1645 patients suffering from ovarian, breast and a variety of other advanced solid tumours had been exposed to olaparib across the dose range 10 mg daily to 600 mg BID, either as monotherapy (n=12 studies) or in combination with other chemotherapy agents (liposomal doxorubicin, cisplatin, dacarbazine, gemcitabine,

gemcitabine+cisplatin, carboplatin, carboplatin+paclitaxel, paclitaxel, topotecan, irinotecan, or bevacizumab).

Olaparib (in the capsule formation) appears to be generally well tolerated in patients with various solid tumours at doses up to and including 400mg bd, as monotherapy. Administration of Olaparib has been associated with reports of laboratory findings and/or clinical diagnoses of:

- Haematological toxicity:
 - Anaemia, generally mild to moderate (CTCAE grade 1 or 2)
 - Neutropenia, predominantly mild to moderate (CTCAE grade 1 or 2)
 - Lymphopenia, generally mild or moderate (CTCAE Grade 1 or 2)
 - Thrombocytopenia, generally mild or moderate (CTCAE grade 1 or 2), sometimes severe (CTCAE grade 3 or 4)
 - Mean corpuscular volume or elevation, generally mild to moderate (CTCAE grade 1 or 2)
- Nausea and vomiting, generally mild to moderate (CTCAE grade 1 or 2), intermittent and manageable on continued treatment
- Dyspepsia, generally mild or moderate intensity (CTCAE grade 1 or 2)
- Dysguesia, generally mild or moderate intensity (CTCAE grade 1 or 2)
- Fatigue, (including asthenia) generally mild or moderate intensity (CTCAE grade 1 or 2)
- Headache, generally mild to moderate intensity (CTCAE grade 1 or 2)
- Dizziness, generally mild to moderate intensity (CTCAE grade 1 or 2)
- Pneumonitis events with no consistent clinical pattern have been reported in a small number of patients with extensive previous exposure to chemotherapy
- Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML) have been reported very rarely in a small number of patients

From the completed studies, there are no safety concerns noted for the renal or hepatic parameters measured and no clinically significant changes of concern relating to coagulation parameters. The changes in haematological parameters (haemoglobin, neutrophils, and thrombocytes) are as expected for olaparib monotherapy or can be explained by co-existing conditions/previous chemotherapy.

Olaparib appears to be generally well tolerated at PARP inhibitory dose levels in the monotherapy clinical studies with predominantly mild toxicity. Thus it represents a potential advance in the treatment of advanced cancers by directly inhibiting PARP-1 and hence tumour growth as monotherapy.

Preliminary data from Phase I and Phase II studies of olaparib in combination with various chemotherapy agents indicate a substantial increase in neutropenia, thrombocytopenia and anaemia compared to giving these cytotoxic agents alone. These findings are consistent with pre-clinical findings. There are more severe haematological events i.e., CTCAE grade 4 neutropenia, febrile neutropenia and thrombocytopenia being reported as SAEs. When these toxicities occur it has been managed with routine clinical practise, including dose delays, dose reductions and intermittent doses and/or the use of supportive care measures such as G-CSF.

Final laboratory data from D0810C00002 (KU36-92) study have shown mean corpuscular volume (MCV) increases in approximately 30% of patients in the study, especially with prolonged treatment with olaparib (≥ 6 cycles of treatment). The MCV elevations were mild to moderate in intensity, observed in the 200 mg BID dose cohort and above and were asymptomatic in nature. There was no obvious correlation of MCV with haemoglobin, platelets or white blood cell (WBC) values for these patients, and there does not appear to be any clinical consequences. MCV has not been captured as a standard laboratory parameter within the olaparib Phase II studies D0810C00008 (KU36-44) and D0810C00009 (KU36-58), however elevations in MCV were also observed in a number of patients from these studies. The MCV elevations again appear to become progressively elevated over time. Elevations in serum amylase were observed in approximately 15% of patients from final laboratory study data from D0810C00002 (KU36-92). The majority of these increases (13%) were mild to moderate (CTCAE grade 1 or 2) with no apparent link to clinical symptoms. No new significant safety information has emerged from any other reported studies with respect to elevations in serum amylase.

Rare Adverse Events

Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML)

As of 27 August 2012 a total of 13 patients who received olaparib have had MDS and/or AML from 5 monotherapy studies (D0810C00002, D0810C00009, D0810C00012, D0810C00019 and D0810C00042) and 2 combination studies (D0810C00004 and D0810C00041) out of a total number of 1896 patients estimated to have received olaparib in the development programme to date (0.7%, 13/1896). Additionally, there have been 2 reports of MDS from 2 monotherapy studies (D0810C00012 [completed], D0810C00019 [ongoing: completed its primary analysis of PFS]) out of 304 patients that received placebo or comparator in the trial programme (0.66%): an AE of MDS was reported in a patient who received placebo in Study D0810C00019 (post PFS data cut-off); and MDS was reported as a secondary cause of death in a patient who received liposomal doxorubicin in Study D0810C00012.

The 13 olaparib-treated patients who reported MDS and/or AML received between 126 days and 1759 days of olaparib for ovarian/peritoneal cancer, prior to the diagnosis of MDS and/or AML. The MDS/AML events occurred post-discontinuation of olaparib treatment in 8 of the 13 patients and 8 patients died. All 13 patients had other potential contributory factors that

may offer an alternative explanation for the development of MDS/AML. Ten patients had a documented BRCA mutation that may predispose them to developing MDS and/or AML (Cole and Strair 2010). The ovarian/peritoneal cancers were diagnosed around 497 days to 4503 days prior to starting olaparib treatment. The majority of patients had been treated with extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents, (ranging from 6 to 95 cycles over periods of 6 months to 15 years). One patient had a family history of leukaemia.

Epidemiological studies from the literature have indicated a higher risk of therapy related MDS/AML in ovarian cancer populations, particularly those who received alkylating agents (Leone et al 1999, Travis et al 1999). Pedersen-Bjergaard et al (Pedersen-Bjergaard et al 1980) reported on the cumulative probability of developing AML over time, from 0 to 5 years of observation, in first line patients with ovarian carcinoma exposed to chemotherapy with alkylating agent Theosulfan. At 2 years the risk was 0.4% (± 0.4 standard error [SE]), at 3 years was 1.0% (± 0.7 SE) and 4 years 2% (± 1.2 SE). This illustrates the increasing risk of developing AML over time when exposed to chemotherapy. The cumulative incidence for developing MDS/AML post exposure to olaparib is currently 13 cases or 0.7% of the total exposed population, where average time from diagnosis of ovarian/peritoneal cancer to onset of the event is 5.9 years (range 2.6 to 12.7). The number of reports falls within those expected using the Pedersen-Bjergaard estimates of patients exposed to chemotherapy.

Pneumonitis

As of 27 August 2012, 1896 patients are estimated to have been exposed to olaparib. There have been 9 (0.5%) reported cases of pneumonitis or suspected pneumonitis.. Three were from monotherapy studies and 6 were from combination studies (3 with olaparib in combination with liposomal doxorubicin, and 1 each with olaparib + topotecan, olaparib + gemcitabine + cisplatin and olaparib + gemcitabine). These patients had a variety of cancer types including breast cancer, nonsmall cell lung cancer, small cell lung cancer and cancer of the thymus. All but one of these patients were hospitalised for the management of pneumonitis. Five of these patients have died; 2 from pulmonary insufficiency and 3 for disease progression. In summary, the 9 reported cases of pneumonitis presented with no consistent clinical pattern and were heavily confounded by a number of predisposing factors (including disease under investigation, underlying pulmonary disease, pre-existing medical conditions, smoking history and/or previous chemotherapy and radiotherapy). Additionally there have been 3 reports of pneumonitis out of 304 patients that received placebo or comparator in the trial programme (0.99%). The frequency of pneumonitis seen with olaparib treatment is consistent with the expected rates of pneumonitis in a cancer population (93-94).

Pre-clinical and Clinical Experience with New Melt-Extrusion (tablet) formulation

Melt-Extrusion (tablet) formulation has been developed to render the olaparib amorphous and presents the drug in a solid dispersion in copovidone (30% drug loading). The milled extrudate is then blended with pharmacopoeial excipients and compressed into a tablet.

The Melt-Extrusion (tablet) formulation, when dosed to fasted dogs at a 100 mg dose, shows at least 2.4 times the C_{max} & AUC than the Gelucire® 44/14 (capsule) formulation. In addition the Melt-Extrusion (tablet) formulation showed reduced pharmacokinetic

variability in the dog with CV of ~ 20% as compared to ~ 50% for the Gelucire® 44/14 (capsule) formulation. It is envisioned that the new Melt-Extrusion formulation of olaparib should provide a more bioavailable and patient friendly formulation by minimising the number of dosage units and providing a more consistent PK profile.

This olaparib Melt-Extrusion formulation (tablet) will be the formulation evaluated in the Phase III clinical programme and consequently this study will also be conducted with the olaparib tablet. There is an ongoing trial (D0810C00024) being conducted at the Royal Marsden NHS Foundation Trust and other centres to establish the comparative bioavailability of the tablet formulation compared with the capsule formulation. In addition single and multiple dose safety & tolerability data will be gathered.

Following single oral dosing with the tablet formulation, absorption was more rapid than the capsule. The C_{max} was typically achieved between 0.5 hours and 2 hours after dosing. Following the peak, plasma concentrations declined biphasically with the mean terminal $t_{1/2}$ of 6.97 hours. The mean volume of distribution of olaparib tablet was 54.9L and the mean plasma clearance was 542L/h. Both G_{mean} , C_{max} and AUC increased approximately proportionally with dose (8-fold and 12-fold, respectively, for a 10-fold increase in dose).

The relative bioavailability (BA) of the tablet formulation (compared to capsule) at the 3 lower dose levels studied are shown in Table 1. At the 2 lower tablet doses, although the C_{max} achieved after dosing with the tablet formulation tended to be higher than that with the capsule, when based on AUC, the BA of the 2 formulations was actually very similar. However, at the highest tablet dose (250 mg), the exposure delivered by the tablet formulation (both C_{max} and AUC) was higher than that delivered by the capsule.

Table 1: Relative bioavailability of tablet versus capsule formulation

Parameter	25mg tablet dose vs 50mg capsule dose	50mg tablet dose vs 100mg capsule dose	250mg tablet dose vs 400mg capsule dose
C_{max} ratio	1.29	1.53	2.49
95% CI	0.92-1.81	1.17-2.00	1.93-3.20
AUC ratio	1.03	0.99	1.74
95% CI	0.83-1.27	0.71-1.38	1.27-2.38

AUC, Area under the plasma concentration-time curve; CI, Confidence interval; C_{max} , Concentration maximum (plasma).

On multiple dosing, a 200mg tablet BID dose gave plasma exposure within the range of those achieved following 400mg BID capsule dose (6.88ug/ml vs 5.71 ug/ml) but the average AUC_{0-12} and C_{min} were lower (36.1ug/ml vs 43.1 ug/mL and 1.00ug/mL vs 1.86ug/mL, respectively) than achieved in a separate cohort of patients following the 400mg BID capsule dose. In addition, steady state data generated from a further cohort of patients randomised to BID dosing with both 200mg tablets and 400mg capsule dose (n=6) demonstrated that the 2 formulations could not be concluded to be bioequivalent (treatment ratio for C_{max} was 0.99 (90% CI:0.85 to 1.15) but for AUC_{0-12} was 0.79 (90% CI:0.65 to 0.94). Following multiple doses at 250, 300, 350 and 400mg BID, exposure continued to increase with dose. Please refer to the IB for further data on the tablet formulation.

The dose escalation phase of the ongoing Phase I bioavailability trial (D0810C00024) has been completed and has shown 400 mg BID to be the maximum tolerated tablet dose with frequent dose limiting toxicities being observed at higher doses. The study is now further evaluating the tolerability and clinical activity of two tablet doses - 300 mg BID and 400 mg BID. Preliminary data suggest that 400mg BID olaparib tablets is well tolerated over the first 4 weeks of treatment. In this trial the starting dose of olaparib tablets will be 400mg BID. It is envisioned that a proportion of patients will require dose reductions to 300mg BID, 200mg BID or 100mg BID respectively for cumulative toxicity over the course of several months of treatment.

4 TRIAL OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to evaluate the anti-tumour activity of olaparib in patients with advanced CRPC who have progressed following one or two chemotherapy regimens including taxane-based regimens.

4.2 Secondary Objectives

The secondary objectives are to evaluate:

- Radiological progression-free survival (rPFS)
- Time to radiological progression
- Progression free survival (PFS)
- Overall survival
- Time to PSA progression
- Duration of PSA response (decline of $\geq 50\%$)
- PSA objective response (PSA-ORR)
- The utility of CTCs as an early indication of benefit from PARP inhibitor therapy
- Further characterise the safety profile of olaparib in advanced CRPC patients

4.3 Tertiary/exploratory Objectives

- To evaluate clinical benefit as indicated by an improvement in pain measurements (BRI-SW)
- To evaluate DW-MRI imaging in selected patients and to correlate these results with PSA, CTC and radiological responses by conventional imaging

5 TRIAL ENDPOINTS

5.1 Primary Endpoints

Response rate:

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

- Objective response by modified RECIST (baseline lymph node size must be ≥ 2 cm to be considered a target lesion) (Appendix E) or
- Conversion of circulating tumour cell count (CTC) from $\geq 5/7.5$ ml blood at baseline to $< 5/7.5$ ml blood nadir confirmed by a second consecutive value obtained four or more weeks later
- PSA decline of $\geq 50\%$ (according to the PCWG2) (Appendix D)

Failure will be defined as:

- Progression by RECIST – increase in measurable lesion size (S) or new lesion AND/OR
- Progression by bone scan (Appendix D)

5.2 Secondary Endpoints

- Radiological progression-free survival (rPFS)
- Time to radiological progression
- Progression free survival (PFS)
- Overall survival
- Time to PSA progression
- Duration of PSA response (decline of $\geq 50\%$)
- PSA objective response (PSA-ORR)
- Proportion of patients with conversion of CTC count to $< 5/7.5$ ml blood nadir
- Safety and tolerability profile of olaparib in patients with metastatic CRPC

5.3 Tertiary/exploratory Endpoints

- Impact of olaparib treatment on bone metastases imaged by DW-MRI in selected patients (optional) and to correlate these results with PSA, CTC and radiological responses by conventional imaging
- Proportion of patients achieving pain improvement

6 TRIAL DESIGN

This study is divided into 2 parts; Part A & B. Part A is an efficacy screening stage for sensitive biomarkers. It is designed as an open-labelled, non-randomised two stage design

both to allow the activity of olaparib in unselected advanced CRPC patients to be evaluated and to permit the development of predictive biomarkers of response to olaparib. Part B is a subsequent validation stage which will be undertaken if confirmation of activity in a biomarker defined subgroup is necessary. It is an open-labelled, single stage assessment of anti-tumour activity of olaparib in preselected patients based on putative biomarkers of HR repair deficiency previously identified in Part A. A total of up to 89 evaluable patients will be enrolled to Parts A & B.

Patients with advanced CRPC who have consented to participate in this trial will be screened and enrolled into either Part A or Part B of the study depending on which part of the study is running at the time of patient enrolment. Patients will be administered oral olaparib tablets, 400mg BID continuously until disease progression is documented and confirmed (i.e., confirmed radiographic progression) or withdrawal for another reason (see section 10.10). Paraffin embedded tumour blocks or sections from the archival tumour tissue at the time of the original diagnosis or from a biopsy / resection of metastatic disease is mandated from all subjects who enrol on the study. These samples should be obtained during the screening period after written informed consent has been obtained. All patients participating in this trial (Part A & B) will also have mandatory circulating tumour cells (CTCs), plasma and fresh tumour biopsies collected at pre-specified times during the study (Table 2). The tumour material will be analysed for biomarkers of sensitivity (response) to PARP inhibition. These tests will include *PTEN* and *ERG* expression, *ETS* gene rearrangements and *PTEN* deletions, markers of cell cycle, DNA damage and repair including geminin expression, RAD51 and gamma H2AX foci formation, etc. Other biomarkers identified to be relevant to HR pathway from other translational research may be studied in parallel. Response to treatment with olaparib will be correlated to all the biomarkers evaluated.

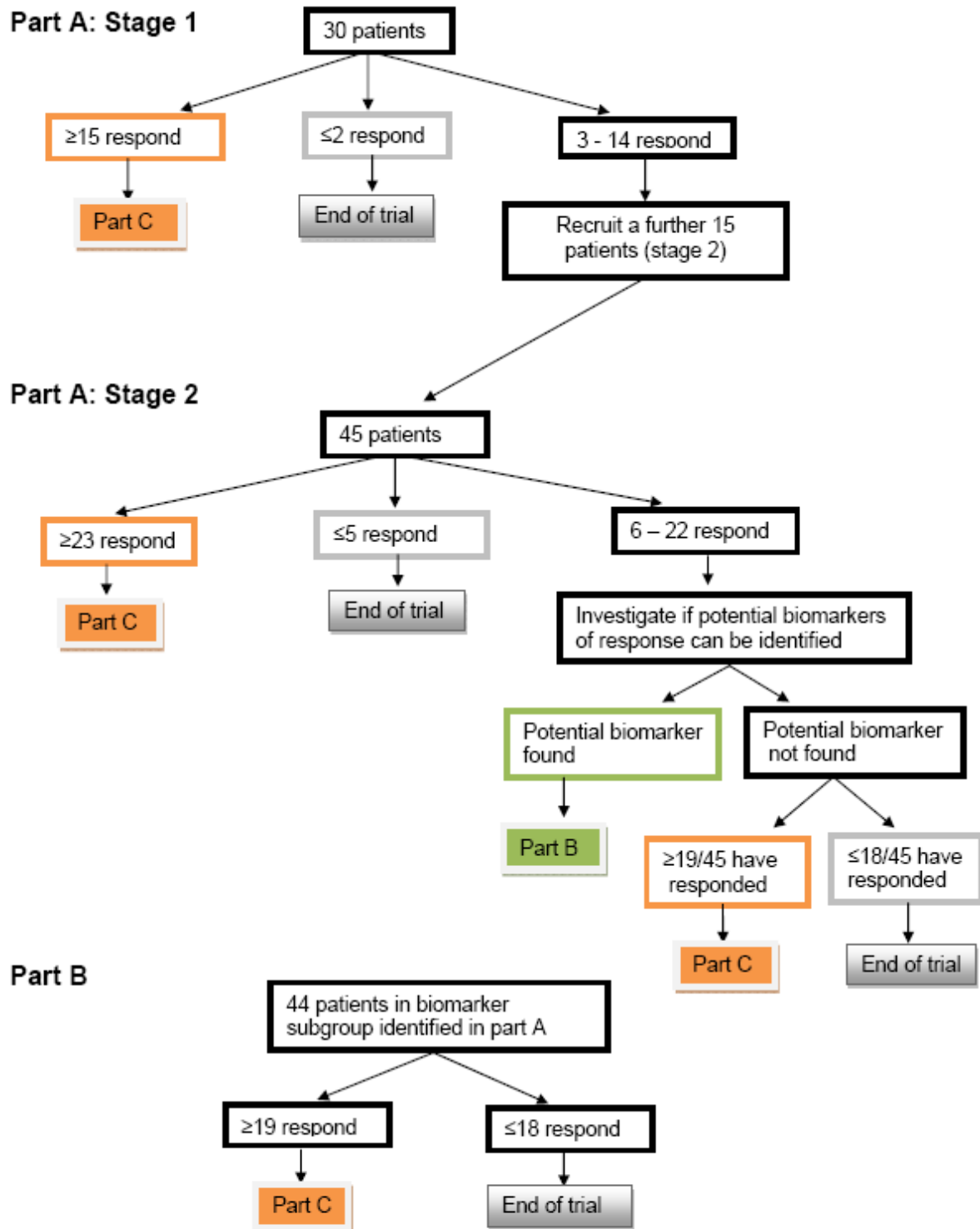
In PART A, accrual will be in unselected patients. The tumour tissue in responders versus non-responders from Part A will be evaluated to develop a molecular classifier for response to olaparib in CRPC patients that can then be utilised to select patients in Part B in the absence of evidence of a high overall response rate in PART A. Patients registered for Part B will be made aware that their tumour tissue will first be analysed for the relevant predefined biomarkers to determine their suitability for participation following consent in Part B of the study.

Disease status will be assessed at regular intervals during the course of the trial by CTC enumeration, computed tomography (CT) scan and / or on magnetic resonance imaging (MRI), diffusion-weighted MRI (DW-MRI), radionuclide bone scans and PSA. Each site should ideally designate the same reader who will evaluate the images for any one patient for the duration of the trial. Throughout the study, safety and tolerability will be assessed by the recording of adverse events; the monitoring of vital signs and physical examinations; and safety laboratory evaluations. Local laboratories will be used for the safety bloods. An independent Data Monitoring Committee (IDMC) will monitor safety data on an ongoing basis. Patient may continue on olaparib for as long as the patient is free of intolerable toxicity and is, in the opinion of the investigator, deriving clinical benefit. Patients may however elect to withdraw from the study at any point without prejudice to further treatment. Patients will have a safety follow-up visit 30 days +/-5 after their last dose of study drug for safety and end of treatment assessments.

Although outlined in the trial schema below, Part C is not currently included in this protocol but may be incorporated following completion of Parts A & B as an amendment to this protocol. PART C will be the subsequent randomised evaluation of olaparib versus an appropriate standard of care comparator to be decided at the time of initiating the amendment. Part C will only be initiated if there is sufficient evidence of antitumour activity observed either in the unselected or selected CRPC patients to warrant further evaluation of olaparib in a randomised setting. This will occur following the evaluation of safety, efficacy and biomarker analysis from Parts A and B by the Independent data Monitoring Committee (IDMC) and will involve a separate funding application and regulatory approvals. Patients in Part C may be either preselected patients based on the molecular determinants of response as identified in Parts A and B, or be unselected, depending on the response that has been seen in Parts A and B.

More details on the design of the trial can be found in the statistical considerations section.

6.1 Study Flow Chart



Part C will only be initiated if the anti-tumour activity observed in Parts A and B are sufficient to warrant a randomised study. The design of Part C will be determined following the analysis of Parts A/B.

Figure 3: Adaptive TOPARP Trial Schema

7 PATIENT SELECTION & ELIGIBILITY

Subjects with advanced progressing CRPC who have had either one or two previous lines of taxane-based chemotherapy will be invited to participate in the TOPARP study.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to safeguard the integrity of the study results.

7.1 Number of Patients

Part A: 30-45

Part B: 44

7.2 Source of Patients

Several oncology centres in the United Kingdom with extensive experience in conducting phase II/III trials have agreed to participate in this trial. Patients who have progressing castration-resistant metastatic prostate cancer will be offered participation in this trial.

7.3 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in the study:

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 archival tumour tissue available for molecular analyses. If the patient does not have a prior histological diagnosis then the planned baseline fresh biopsy may be used for both the purpose of confirming the histological diagnosis prior to trial entry and for subsequent biomarker analysis. All patients must be willing to have fresh biopsies to obtain tumour tissue for biomarker analysis
4. At least one but no more than two previous taxane-based 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:
 - At least 28 days since the completion of prior flutamide treatment. Patients whose PSA did not decline in response to antiandrogens given as a second line or later intervention will only require a 14 days washout prior to Cycle 1, Day 1.
 - 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.

- 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:
 - 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 $\mu\text{g/L}$ (2 ng/ml); patients on systemic glucocorticoids for control of symptoms must have documented PSA progression by PCWG22 while on systemic glucocorticoids prior to commencing Cycle1 Day1 of treatment.
 - 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 $\geq 50\%$)
 9. Life expectancy > 12 weeks.
 10. Patient must be able to swallow a whole tablet.
 11. Patient and the patient's partner of childbearing potential, must agree to use medically accepted methods of contraception (e.g., 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 CTC count of ≥ 5 cells/7.5mls blood at screening confirmed by the central laboratory.
 14. Subjects must have adequate bone marrow, hepatic and renal function documented within 7 days of registration, defined as:
 - Haemoglobin $\geq 10\text{g/dL}$ independent of transfusions for 14 days if related to anaemia due to advanced prostate cancer. If not, subjects should be independent of transfusions for 28 days.
 - White blood cells $> 3 \times 10^9/\text{L}$
 - Absolute neutrophil count $\geq 1.5 \times 10^9/\text{L}$
 - Platelets $\geq 100 \times 10^9/\text{L}$
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) except for patients with known Gilbert's syndrome.
 - Aspartate transaminase (AST) (SGOT) and alanine transaminase (ALT) (SGPT) ≤ 2.5 x ULN or ≤ 5 x ULN in the presence of liver metastases.
 - Serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance $> 40\text{mL/min}$ for patients with creatinine levels above institutional normal. For GFR estimation, the Cockcroft and Gault equation should be used:
$$\text{GFR} = \text{CrCl (ml/min)} = (140 - \text{age}) \times \text{wt (kg)} / (\text{serum creatinine} \times 72)$$
 - Albumin > 25 g/l

7.4 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

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 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 have experienced a seizure or seizures within 6 months of study treatment or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in patients not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital (see Section 12.13)).
11. Patients receiving any of the following classes of inhibitors of CYP3A4 (see Section 12.13 for guidelines and wash out periods);
 - 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 investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's 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

7.5 Restrictions

1. Patients must refrain from fathering a child or donating sperm during the study and for 3 months following the last dose of olaparib. Patients of child bearing potential and their partners, who are sexually active must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after the last dose of study drug. Reliable methods of contraception should be used consistently and correctly. Acceptable methods of contraception to be used in this study include:
 - Condom with spermicide and one of the following:
 - Oral contraceptive or hormonal therapy (e.g. hormone implants)
 - Placement of an intra-uterine device
 - Acceptable non-hormonal birth control methods include:
 - Total sexual abstinence. Abstinence must be for the total duration of the study and for 3 months following the last dose of olaparib
 - Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
 - Tubal occlusion plus male condom with spermicide
 - Intrauterine Device (IUD) plus male condom and spermicide - Provided coils are copper-banded
 - Acceptable hormonal methods:
 - Etonogestrel implants (e.g., Implanon, Norplan) and male condom with spermicide
 - Normal and low dose combined oral pills+male condom with spermicide
 - Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
 - Intravaginal device and male condom with spermicide (e.g., EE and etonogestrel)
 - Cerazette (desogestrel) and male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.
2. No other chemotherapy or other anticancer treatment is to be permitted with the exception of continued used of LHRH agonist, during study participation. If possible, initiation of a new line of treatment will not be earlier than 30 days post date of last dose. At least a 10 day washout period of olaparib is recommended to ensure patient safety. Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be adequately be managed with analgesics as long as the patient does not meet the criteria of disease progression or treatment discontinuation.
3. Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

4. In vitro data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, **to ensure patient safety all patients must avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity** (see Section 12.13) from the time they enter the screening period until 30 days after the last dose of study medication.

8 OVERVIEW OF STUDY PROCEDURES

8.1 Informed Consent

The study objectives, overall requirements, potential benefits and risk will be discussed with potentially eligible patients. Interested patients will be given a TOPARP patient information sheet. Consent must be obtained only after allowing the patient sufficient time for consideration, and the opportunity to ask any further questions. A signed, TOPARP written informed consent form must be obtained from the patient in accordance with local practice and regulations. Pre-entry tests, not performed routinely as part of standard patient management, will only be done after the TOPARP consent form has been signed and personally dated by both the patient and the Investigator. Confirmation of the patient's informed consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed form will be provided to the patient and the original retained in the investigator site file and must be available for verification by ICR-CTSU study staff or for regulatory audit/inspection at any time. Patients who consent on the TOPARP study, consent to having fresh tumour biopsies, archival tumour tissue, CTCs and plasma collected for molecular and biomarker studies. Please refer to section 15.8 regarding consent for genetic testing.

Patients who wish to have diffusion weighted MRI (DW-MRI) scans to assess their disease during the study will be required to sign a specific DW-MRI consent form. Participation in this component of the study is entirely voluntary. Refusal to participate in the DW-MRI component of the study will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.

8.2 Registration

Once informed consent has been obtained, patients must be registered for screening by contacting the ICR CTSU:

To register a patient telephone ICR-CTSU
On: 0208 643 7150
(09.00 – 17.00 Monday to Friday)

The following information will be required when registering the patient:

- Name of cancer centre, treating hospital, consultant and person registering patient

- Confirmation that patient has given written informed consent
- Patients initials and date of birth
- Confirmation of diagnosis

The patient will be allocated a unique registration number.

8.3 Eligibility status and trial entry

Once all screening evaluations have been completed, an eligibility checklist should be completed by the clinician/research nurse. The eligibility checklist should be completed for all patients registered.

For those patients who remain eligible, the clinician / research nurse should contact ICR-CTSU to confirm eligibility and obtain a trial number.

To confirm patient eligibility telephone ICR-CTSU

On: 0208 643 7150

(09.00 – 17.00 Monday to Friday)

The following information will be required:

- Patient's full name, hospital number, NHS number, postcode and trial registration number.
- Confirmation of the patient's eligibility status according to the eligibility checklist
- Confirmation that the evaluable disease being followed in the trial has been assessed by either CT or MRI and a bone scan within 28 days of scheduled start date of treatment
- Confirmation of consent for the trial

If the patient is confirmed as eligible for trial entry, the caller will be given the patient's unique trial identification number (Trial ID), and fax confirmation will be sent to the appropriate pharmacist to enable dispensing of the study drug.

A screening log should be completed for all registered patients who do not subsequently enter the study. This will record reasons for exclusion e.g. because screening tests identified that they were ineligible or the patient subsequently withdrew consent.

9 OVERALL STUDY ACTIVITIES

9.1 Screening Period

All patients must sign the TOPARP written informed consent before study specific screening procedures can be performed. Consent may be obtained up to 28 days prior to

Cycle 1, Day 1. Patients will have a screening period of up to 28 days prior to Cycle 1 Day 1. The laboratory investigations (haematology, electrolytes, tumour markers and testosterone level) must be performed within 14 days of starting treatment on olaparib. Results of CTC enumeration performed at the central laboratory in blood samples collected within 28 days of starting treatment will be acceptable. For details of the schedule and nature of the screening assessments, refer to Table 2 (page 56). All the screening assessments must be complete and eligibility criteria met prior to enrolment into the study. Patients who meet the eligibility and screening requirements will return to the site for Cycle 1 Day 1 visit. As part of the screening process, CTCs, a pre dose biopsy and blood samples will be collected for the predefined biomarkers of interest.

9.2 Treatment Period

All screening assessments must be completed and reviewed prior to the commencement of Cycle 1 Day 1 assessments. In the event that Screening and Cycle 1 Day 1 visits coincide, Cycle 1 Day 1 assessments do not need to be repeated. Olaparib at a dose of 400mg will be administered orally twice daily, once in the morning and once in the evening, continuously. Patients may receive continuous treatment for as long as they remain free from intolerable toxicity, and, in the investigator's opinion, are receiving clinical benefit. The patient will return on Day 8 and Day 15 of Cycle 1 and subsequently on the first day of each treatment cycle in order to evaluate safety, tolerability and dosing compliance. From Cycle 2 to end of study treatment patients' Day 1 visits will occur on a 28 day cycle with a +/- 2 day window. If the study window is utilised every effort will be made for the patient to return to schedule. Patients will have additional imaging visits up to 8 days before Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1, after every 3 cycles thereafter and treatment discontinuation. For details of the schedule and nature of the on-going assessments, refer to Table 2. The dose of olaparib may be reduced and/or a treatment delayed in patients experiencing toxicities according to the dose modification guidelines as set out in section 12.8. Safety parameters will be continuously followed-up during the duration of the trial.

9.3 End of Treatment (EOT) Visit

All patients will return for an end of treatment visit 30 +/-5 days from the time of last dose of treatment or prior to the start of next therapy, whichever happens first for safety and end of study treatment assessments. For details of the schedule and nature of the assessments for this end of study treatment visit, refer to Table 2 and section 11.2.5.

9.4 Follow Up Visits

Following treatment completion, patients will be followed for survival every 3 months.

10 OVERALL TRIAL ASSESSMENTS

10.1 Clinical Measurements

The Investigator will ensure that all data collected in the study are provided to ICR-CTSU. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the Electronic Case Report Form (eCRF) in accordance with instructions provided.

10.2 Medical History

Medical and Surgical History

Medical and surgical history, including a history of the disease being studied, other significant past and on-going conditions should be recorded. All previous radiotherapy and chemotherapy, as well as any other therapy received for prostate cancer, must be documented.

Recording of Concomitant Medications

The use of or any change in the patient's concomitant medications will be recorded when the patient visits the hospital (including a review of the patient's diary card for any self-administered medication).

Current Signs and Symptoms

Current signs and symptoms of the disease will be recorded, together with the appropriate NCI-CTC grade and causality, if appropriate.

10.3 Physical Examination

Evaluations should be performed by the same evaluator throughout the study whenever possible. A full physical examination will include the assessment of the body systems listed below and reporting if these findings were normal, abnormal or not done. A full examination will be conducted at the screening visit, cycle 1 day 1 and the end of study treatment visit. At all other times the extent of the examination beyond vital signs and weight will be conducted as clinically indicated. Height will be recorded at screening visit only. Vital signs include blood pressure, heart rate, respiratory rate, and oral or aural body temperature.

The following must be assessed and recorded:

- General appearance
- Cardiovascular
- Respiratory
- Gastrointestinal

- Genitourinary
- Central Nervous System
- Dermatological
- Musculoskeletal
- Peripheral lymph nodes
- Other

10.4 ECG Monitoring

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the Investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. An ECG assessment will be performed at screening as a baseline assessment. Subsequent ECGs will only be performed if clinically indicated.

10.5 Brief Pain Scores

The BPI-SF will be self-administered in the clinic to the patients on the first day of each treatment cycle and the results recorded in the patient's notes (Appendix I)

10.6 Blood, Tissue and Other Sampling

Blood samples for safety assessments will be done at the local institutes. Tests relating to biomarker work on CTC, plasma and tumour material will be performed primarily at The Institute of Cancer Research Cancer Biomarkers Laboratory. Samples will be collected and processed according to specified detail in the TOPARP Laboratory Manual. There may be a requirement to send some of the samples to be processed in a different laboratory. This will be done with contractual agreements in place and patient details will remain confidential.

Bone marrow or blood cytogenetic analysis may be performed according to standard haematological practice for patients with prolonged haematological toxicities as defined in Section 3.3. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to ICR-CTSU (see section 13).

Routine clinical laboratory tests will include the following;

Table 1: List of Laboratory Tests

Local Laboratory Tests		
<p>Haematology:</p> <ul style="list-style-type: none"> • Neutrophils • Haemoglobin (Hgb) • Platelet count with differential • White blood cell (WBC) count • Lymphocytes • Coagulation Factors: Prothrombin Time (PT), Partial Thromboplastin Time (PPT), International Normalized Ratio (INR) 	<p>Serum Chemistry:</p> <ul style="list-style-type: none"> • Albumin (ALB) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT;SGPT) • Gamma-glutamyltransferase (GGT) • Amylase • Aspartate aminotransferase (AST;SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Chloride (Cl) • Creatinine (Cr) • Glucose • Lactate dehydrogenase (LDH) • Magnesium • Phosphate • Potassium (K) • Sodium (Na) • Total bilirubin • Total protein • Uric acid • Bicarbonate 	<p>Urinalysis dipstick for:</p> <ul style="list-style-type: none"> • Blood • Protein • Glucose • (Microscopic examination if abnormal) <p>Additional laboratory tests:</p> <ul style="list-style-type: none"> • Prostate specific antigen (PSA) • Serum testosterone <p>In the event of protracted myelosuppression:</p> <ul style="list-style-type: none"> • Bone marrow or blood cytogenetic analysis
Central Laboratory Tests		
<ul style="list-style-type: none"> • Circulating Tumour Cells (CTCs) for enumeration & molecular characterisation • Circulating tumour DNA 	<ul style="list-style-type: none"> • Circulating tumour microRNA (miRNA) • Plasma for biomarkers 	<ul style="list-style-type: none"> • Mandatory tumour biopsy • Urine telopeptides

10.7 Efficacy Measurements

CT or MRI Scan Assessments (Modified RECIST)

Baseline contrast-enhanced CT of the chest, abdomen and pelvis should be performed for the assessment of measurable lesions. Where contrast is contraindicated then either an MRI of the chest, abdomen and pelvis or a non-contrast CT scan can be performed if the

measurable disease is easily discernable without contrast. All baseline CT will be performed during the 28-day screening window as close as possible to Cycle 1, Day 1 of treatment. The CT scans will be repeated up to 8 days before Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3rd cycle subsequently (Table 2). CT scans may be performed earlier if clinically indicated. Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed for the purposes of the study if they were performed within the correct time frame and are of sufficient quality. Subsequent, repeat imaging requires the same method of assessment to characterise each identified lesion at baseline and during follow-up. Response categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) (refer to Appendix E) will be assigned at the scheduled visits. In the case of stable disease, measurements must have met the stable disease criteria at least once after study start for a minimum interval of 12 weeks. PR or CR by RECIST must be confirmed with a repeat tumour assessment 4 weeks after the criteria for response was met.

For the purposes of analysis, overall response using Investigator measurements of target lesions, assessment of non-target lesions and new lesions collected on the eCRF to derive the best overall response, and other protocol endpoints using these data. All medical images and tumour response assessments will be collected and retained on site as source data. A central image review may be performed by the sponsor if required.

Bone Scan Assessments

Bone scans will be used to assess bone lesions. Baseline bone scans will be performed during the 28 day screening window as close as possible to Cycle 1 Day 1, and up to 8 days prior to Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3rd cycle subsequently (Table 2). Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed as the baseline study if they were performed within the correct time frame and are of sufficient quality. **Bone deposits will be reported as absence or presence of new bone lesions. New lesions at the first scheduled reassessment at Week 12 must be confirmed by a second scan performed 6 or more weeks later. Disease progression by bone scan will be defined as two new bone lesions at the first 'progression' scan, confirmed by a further scan at least 6 weeks later (see section 10.9 for more details).** All medical images and tumour response assessments will be collected and archived locally. A central image review may be performed.

Diffusion weighed-MRI (DW-MRI) Scan Assessments

DW-MRI constitutes an optional component of the study. DW-MRI provides additional information regarding tumour cellularity and tumour cell death that cannot be evaluated with other imaging techniques. DW-MRI will be obtained at baseline (screening), up to 8 days prior to Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and every 3 cycles subsequently. These results of these scans will not be utilized for the purpose of assigning disease status. Patients who wish to participate in this optional component of the study will be required to sign a separate Patient Informed Consent Form (PICF).

PSA Measurements

PSA will be assessed at baseline and routinely on day 1 of every 3rd cycle (12 weeks) by PCWG2 criteria (refer to Appendix D). Increases and decreases will be tracked in order to assess PSA responses. PSA changes from baseline to 12 weeks (either increment or decline) and maximal change in PSA will be recorded. Responses by PCWG2 criteria must be confirmed 28 days later.

Although serial PSA will be measured on this study and PSA progression documented by the PCWG2 criteria, the PSA value on its own is not considered a reliable measure of clinical benefit and does not correlate tightly with survival. PSA flares may occur early in the treatment and may therefore confound response assessment. Additionally, there is emerging data that PARP-1 is implicated in multiple other essential cellular functions separate from DNA repair including *ETS* gene-mediated transcription regulation which may have a bearing on the response assessments by PSA. PSA reading should not be applied as the sole criteria to consider treatment discontinuation. In absence of evidence of radiological or clinical evidence of disease progression, patients should continue in the study despite an increment in PSA. **Overall, therefore patients will not be taken off trial purely for rising PSA levels in the absence of worsening scans and symptoms since PARP inhibitors are likely to impact tumour growth without impacting PSA secretion.**

PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG2 criteria:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA from screening (baseline) PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- For patients with PSA declines at Week 13, the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. For patients with no PSA declines at Week 13, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented, which is confirmed by a second consecutive value four or more weeks later.

CTC Conversion Rate

CTCs will be obtained at various time points before, during and after treatment for enumeration and molecular characterisation (Table 7). CTC enumeration will be performed at The Institute of Cancer Research laboratories using the analytically valid CellSearch system (Veridex, LLC). For patients with baseline CTC counts of ≥ 5 cells/7.5 ml of blood, a conversion is defined as a nadir decline in the CTC count to < 5 cells/7.5 ml of blood. The conversion of CTC counts that are ≥ 5 to < 5 and percentage decline of $\geq 30\%$ indicative of clinical benefit and improved survival outcome will be measured (76,77,78).

A central review of bone scans and CT scans will take place. Anonymised copies of bone and CT scans should be sent to ICR-CTSU for central review on their request.

10.8 Safety Measurements

Safety parameters will be continuously assessed throughout the study prior to each cycle of treatment. These will include:

- Medical history, vital sign measurements, physical examination, and body weight
- Haematology, clinical chemistry, urinalysis
- Eastern Cooperative Oncology Group (ECOG) performance status
- Assessment of concomitant medications
- Adverse events (AEs) and serious adverse events (SAEs) including laboratory test AEs will be graded and summarised according to the NCI CTCAE version 4.02

10.9 Criteria For Discontinuation Of Study Treatment

The consensus guidelines of the PCWG2 recommend that confirmed radiographic progression is the most reliable indicator of clinical benefit in patients with CRPC. Based on this consideration, patients should be maintained on study treatment until confirmed radiographic progression or clinical progression or if the treating physician decides to initiate new systemic anti-cancer therapy. It is recommended that if the patient has PSA progression but no unequivocal clinical or radiological progression and an alternate treatment is not indicated, the investigators should maintain the patient's treatment until radiological disease progression is documented and confirmed. However, if the patient has unequivocal clinical progression without radiographic progression, these patients could be considered for other therapy at the discretion of the treating physician. In this circumstance, study treatment should be stopped and the patient advised regarding available treatment options. The intent of these criteria is to maintain study treatment for patients with PSA progression, given the absence of alternative treatment options available to participants who have failed both castration and chemotherapy and the high likelihood that some clones of prostate cancer may be benefiting in the context of radiological stability despite a PSA rise.

A patient is considered to have progressed on study if one or more of the following findings occur:

1. Progression by bone scan:

- The first bone scan with ≥ 2 new lesions compared with baseline is observed ≤ 13 weeks from cycle 1 day 1 and is confirmed by a second bone scan taken ≥ 6 weeks later showing 2 additional new lesions (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan)
- The first bone scan with ≥ 2 new lesions compared with baseline is observed > 13 weeks from cycle 1 day 1 and the new lesions are verified on the next bone scan ≥ 6 weeks later (i.e. a total of ≥ 2 new lesions compared with baseline).

2. Progression of soft tissue /visceral disease by modified RECIST:

- A patient will be determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions by modified RECIST. **Lymph nodes have to be >2 cm in size to be deemed measurable.**

3. Unequivocal evidence of clinical progression:

A patient can be taken off study at the discretion of the treating physician under the following circumstances:

- Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumour progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to grade 3 or higher felt by the investigator to indicate clinical progression
- Felt to be in the best interest of the patient to come off study due to clinical progression

4. Death from any cause.

When study treatment is discontinued due to unequivocal clinical progression, attempts should be made to determine the patient's status at the End of Treatment Visit to assess for radiographic progression, including a confirmatory bone scan, as deemed appropriate by the treating team.

10.10 Withdrawal from Study Treatment

Criteria for withdrawal of study treatment are outlined below:

1. Patient Withdraws Consent

Patients have the right to withdraw from the study at any time, without prejudice to their medical care, and are not obliged to state their reasons. If the patient withdraws consent, he should be encouraged to have a complete End of Treatment (EOT) visit and effort should be extended to clarifying the reason for the withdrawal.

Investigator may choose to withdraw a patient at any point if this is considered to be in the patient's best interest. The patient must be discontinued from the study treatment due to any of the safety reasons outlined below:

2. Sustained or Recurrent Unacceptable Side Effects:

- Any grade 3 or 4 events that have not reverted to grade 1 or the baseline (Cycle 1 Day 1) grade after a 42 days break off treatment with appropriate medical intervention. At the Investigator's discretion, patients may be considered for dose reductions [see Section 12.8 for management of toxicity & dose adjustments, providing they have not already undergone 2 dose reductions to 300 mg BID and 200 mg BID. If the grade 3 or 4 adverse events recurs at the lowest dose level (100 mg BID) then the patient must be discontinued].
- Unacceptable adverse events or any other toxicity in the investigator's opinion.
- Serious intercurrent illness or significant worsening of intercurrent illness that prevents further administration of treatment.
- A severe drug reaction or a hypersensitivity reaction to olaparib.

3. Non-compliance with Dosing or Trial Protocol Requirements

Patient is unable to adhere to study visit schedule or comply with protocol requirements despite several reminders about the requirements and efforts made to identify and resolve the aetiology of the problem may be discontinued at the discretion of the Investigator.

4. Progressive Disease

Evidence of clinically significant progressive disease as defined in section 10.9.

5. Use of Prohibited Concurrent Medication

The patient will be discontinued from the protocol treatment when prohibited drug is administered. Supportive care medications are permitted with their use following institutional guidelines.

6. Other Reasons

Additionally, patients may be discontinued from study treatment for any of the following reasons:

- Patient lost to follow-up
- If in the opinion of the Investigator, a change of therapy would be in the best interest of the patient
- Major protocol violation
- Incorrectly enrolled patients, i.e., the patient does not meet the required inclusion/exclusion criteria for the study

Attempts should be made to contact any patient failing to return for a scheduled visit/follow up, in order to ensure that the reason for not returning is not an adverse event. Likewise attempts should be made to establish whether any patient declaring a desire to discontinue

from the study e.g. for personal reasons, is in reality due to an adverse event (AE). If the olaparib therapy is prematurely discontinued, the primary reason for discontinuation must be recorded in the appropriate section of the eCRF. Patients will be required to attend an end of treatment visit at least 30 +/- 5 days after discontinuing study medication for collection and/or completion of AE information. All new events occurring during this 30-day period must be recorded (if SAEs they must be reported to the ICR-CTSU within 24 hours) and followed-up to resolution, unless in the opinion of the Investigator, the condition is unlikely to resolve due to the patients' underlying disease. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the Investigator assesses as possibly related to the study medication should also be reported as an AE. The patient should return all study medication following cessation of the study drug.

In the unlikely event that a patient withdraws consent for further follow-up data to be collected, the appropriate form in the eCRF should be completed and returned to ICR-CTSU. Clarification should be sought to ensure that the patient is not simply withdrawing from study drug. In the extremely unlikely event that the patient wishes to have their data removed from the trial completely (the implications of this should be discussed with the patient to ensure that this is their intent), this should be indicated as such on the form.

10.11 Patient Replacement Policy

An evaluable patient is defined as a patient who:

- Meets all of the inclusion and exclusion criteria specified in Sections 7.3 and 7.4 within the specified time frame;
- Has adequate histological tissue for the biomarker analysis.
- Completes twelve weeks of treatment with olaparib or experiences an event defined as treatment failure within twelve weeks.

Patients who prematurely withdraw from the study for reasons other than treatment failure may be replaced. Patients who become non-evaluable e.g. by ceasing to take LHRH agonists, may also be replaced. Replacement of ineligible and non-evaluable patients will be dependent on authorisation by the Independent Data Monitoring Committee (IDMC)

Note: Rising PSA or worsening bone scans in the first 12 weeks is NOT treatment failure and may reflect a flare response.

11 TRIAL ASSESSMENTS BY VISIT

Access to the electronic case report form (eCRF) will be provided by ICR-CTSU for each patient eligible for the trial. The relevant eforms should be completed at each hospital visit.

Note: some of the scheduled blood samples collected at screening, C1D1, C1D8, C2D1, C3D1, C6D1 and end of treatment require the patient to be fasted for 8 hours prior to sampling (see section 14.3 for further details).

11.1 Baseline Assessments

11.1.1 Screening

Screening activities that involve imaging, CTCs and collection of archival and fresh tumour tissue will be conducted within a 28-day window prior to commencing Cycle 1 Day 1. All other screening activities/procedures outlined below will be conducted during the screening period over 14-days prior to Cycle 1 Day 1.

- Obtain archival tissue for analysis of biomarkers (Days -28 to Day 1). Previous biopsy samples taken prior to TOPARP consent but processed as per the TOPARP Laboratory Manual may be used if within the appropriate window. Please refer to section 15, for further details of specimens to be collected.
- Obtain mandatory fresh tumour biopsy (Days -28 to Day 1). Please refer to section 15, for further details of specimens to be collected.
- Medical history including details of the following:
 - All co-morbidities
 - Oncology history / family history of cancers
 - Prior prostate cancer history including extent of disease (stage), Gleason score at diagnosis, PSA levels
 - Previous hormonal, cytotoxic, and experimental treatments with start and stop dates
- Demographics
- Listing of current baseline signs and symptoms with associated NCI Common Terminology Criteria for Adverse Events grading (0-4)
- Physical examination
- Weight, and height
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Assessment of ECOG Performance Status
- 12 lead ECG
- Local Laboratory tests:
 - FBC: WBC with differential count, RBC, haemoglobin, hematocrit, platelets.
 - Coagulation studies (PT/PPT, INR)
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST,

- ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, uric acid, and magnesium
 - Urinalysis: routine dipstick. Only if the dipstick is abnormal will the urine be sent for analysis
 - PSA: If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE
 - Serum testosterone
- Baseline tumour assessment
 - CT and / or other imaging procedures as clinically indicated
 - Bone Scan
 - DW-MRI (optional)
- Pain (BFI-SF) and Analgesic Usage Score
- Concomitant medications listing
 - Obtain a complete list of all prescription and nonprescription (over the counter) medications currently taken including pain medications. This also includes any nutritional supplements and/or herbal preparations.
- Assessments of signs and symptoms
- Research Biomarkers
 - Circulating Tumour Cell (CTC) blood collection for enumeration and molecular characterisation (Days -28 to Day 1). Blood samples taken prior to TOPARP consent may be used for CTC enumeration if within the appropriate window and enumeration was performed at the central laboratory.
 - Circulating Plasma DNA and RNA studies
 - PAXgene miRNA studies
 - Urine markers of bone turnover and RNA
 - Serum Proteomic studies
 - Plasma and urine metabolomics studies
 - Buccal swab for DNA studies
 - Saliva for DNA studies

11.1.2 Cycle 1 Day 1

Patients who are eligible after screening and who accept to be entered into the study should be entered within 28 days of informed consent. All the screening assessments should have been completed and screenings results reviewed prior to trial entry and the commencement of Cycle 1.

The following procedures should be carried out **prior to dosing of study treatment**:

- Update listing of current baseline signs and symptoms with associated NCI Common Terminology Criteria for Adverse Events grading (0-4)
- Updated oncology history with any events that may have transpired since screening
- Physical examination
 - Full examination
 - Vital signs including blood pressure, heart rate, respiratory rate, oral body

- temperature
 - Height and weight
- Assessment of ECOG Performance Status
- Local Laboratory Tests:
 - FBC: WBC, RBC, haemoglobin, haematocrit, platelets with differential count.
 - Coagulation studies (PT/PPT, INR)
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, uric acid.
 - Urinalysis: routine dipstick. Only if the dipstick is abnormal will the urine be sent for analysis.
 - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
- Pain (BFI-SF) and Analgesic Usage Score
- Concomitant medications listing
 - Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations
- Assessment of adverse events
- Research Biomarkers
 - Circulating Tumour Cell (CTC)
 - Circulating plasma DNA and RNA studies
 - PAXgene miRNA studies
 - Urine markers of bone turnover (telopeptides) and RNA
 - Serum proteomic studies
 - Plasma and urine metabolomics studies

11.2 On-treatment Assessments

11.2.1 Cycle 1 Day 8 Visit

The following assessments should be carried out on Day 8:

- Brief history and physical examination as clinically indicated
- Vital signs including blood pressure, heart rate, respiratory rate, oral body temperature
- Assessment of ECOG Performance Status
- Local Laboratory Tests:
 - Full blood count including WBC, haemoglobin, platelets
 - Coagulation studies (PT/PPT, INR)
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, uric acid, magnesium
- Concomitant Medications listing:

- Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations
- Adverse events will be monitored throughout the study. At each post-baseline visit, the investigator will begin by querying for adverse events by asking each patient a general, non-directed question such as ‘How have you been feeling since the last visit?’ Directed questioning and examination will then be done as appropriate.
- Dosing compliance check
- Obtain post treatment mandatory fresh tumour tissue biopsy (Cycle 1 Days 8 to Day 28)
- Research Biomarkers
 - Circulating Tumour Cells (CTC)
 - Circulating plasma DNA and RNA studies
 - Plasma and urine for metabolomics studies

11.2.2 Cycle 1 Day 15 Visit

- Research Biomarkers
 - Circulating Tumour Cells (CTC)

11.2.3 Day 1 of Cycles 2, 3, 5, 6, 8, 9, 11, and 12 (Continue every cycle beyond Cycle 12)

The following assessments should be carried out at the indicated time point:

- Brief history and physical examination as clinically
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature
- Weight
- Assessment of ECOG Performance Status
- Concomitant Medications listing
 - Update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations.
- AE evaluation and recording at each post-baseline visit
- PSA measurements will be conducted every 12 weeks. PSA results will be assessed according to PCWG2 criteria
- Dosing compliance check and a count of study medication will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not 100% in the absence of toxicity, patient should be re-instructed regarding proper dosing procedures
- Pain (BFI-SF) and Analgesic Usage Score (each cycle)

- Local Laboratory Tests:
 - FBC: WBC, RBC, haemoglobin, haematocrit, platelets with differential count
 - Coagulation studies (PT/PPT, INR)
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, LDH, uric acid, magnesium
- Research Biomarkers
 - CTC collection (Cycles 2, 3, 4, 7, every 3rd cycle thereafter and at treatment discontinuation/EOT)
 - Plasma for DNA, RNA studies (Cycles 2, 3, 5 and at treatment discontinuation/EOT)
 - Paxgene miRNA studies (cycle 3, 5 and at treatment discontinuation/ EOT)
 - Urine and plasma metabolomics (cycles 2, 3 ,6 and at treatment discontinuation/EOT)
 - Urine markers of bone turnover and RNA (cycle 3, cycle 6 and at treatment discontinuation/ EOT)

11.2.4 Cycles 4, 7, and 10 and Treatment Discontinuation (continue every 3rd cycle beyond Cycle 10)

In preparation for the study visit, the following assessments should be conducted up to 8 days prior to the indicated visit. Results should be available for review at the Cycle 4, 7, or 10 Day-1 visit and every 3rd cycle beyond Cycle 10.

- CT Scan
- Bone Scan
- DW-MRI (optional)
- Other imaging procedures should be conducted as clinically indicated

At the study visit the following assessments should be conducted:

- Brief history and physical examination as clinically indicated
- Vital signs including blood pressure, heart rate, respiratory rate and oral body temperature.
- Weight
- Assessment of ECOG Performance Status
- Local Laboratory Tests
 - FBC: WBC, RBC, haemoglobin, platelets with differential count, chemistry with electrolytes: sodium, potassium, chloride, carbon dioxide, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, glucose, LDH, uric acid, magnesium, random glucose.
 - Coagulation studies (PT/PPT, INR)
 - PSA (every 12 weeks): If patient undergoes a DRE, then PSA must be sampled prior to the DRE

- Concomitant medications listing
- AE evaluation and recording
- Dosing compliance check
- Pain (BFI-SF) and Analgesic Usage Score (each cycle)
- Review of imaging results (CT and bone scan) should be conducted and disease response /progression ascribed at the actual study visit (Cycle 4, 7, or 10 Day 1) unless otherwise indicated.
- Tumour biopsy (this end of study treatment biopsy is optional and can be collected at any point from treatment discontinuation up to the end of treatment visit).
- Research Biomarkers
 - CTC collection (Cycles 2, 3, 4, 7, every 3rd cycle thereafter and at treatment discontinuation/EOT)
 - Plasma for DNA, RNA studies (Cycles 2, 3, 5 and at treatment discontinuation/EOT)
 - Paxgene miRNA studies (cycle 3, 5 and at treatment discontinuation/EOT)
 - Urine and plasma metabolomics (cycles 2, 3, 6 and at treatment discontinuation/EOT)
 - Urine markers of bone turnover and RNA (cycles 3, 6 and at treatment discontinuation/EOT)
 - Serum proteomic studies (at treatment discontinuation/EOT)

11.2.5 End of Treatment (EOT) Visit

Patients should return for an EOT visit 30 days +/- 5 following the patient's last dose of drug or prior to starting a new line of anticancer treatment, whichever occurs first. The following assessments should be carried out at the EOT visit:

- Physical examination and weight
- Vital signs including blood pressure, heart rate, respiratory rate, and oral or aural body temperature.
- Assessment of ECOG Performance Status
- 12-lead ECG is not mandated but should be done if clinically indicated
- Local Laboratory tests:
 - FBC: WBC, haemoglobin, platelets with differential count
 - Coagulation studies (PT/PPT, INR)
 - Chemistry with electrolytes: sodium, potassium, chloride, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, amylase, calcium, phosphate, random glucose, LDH, uric acid, magnesium.
 - PSA: If patient undergoes a DRE, PSA must be sampled prior to the DRE.
 - Disease Progression Assessment Review of imaging (CT, Bone scan, DW-MRI) results assessment according to modified RECIST and PCWG22 criteria.
 - Review of PSA results conducted over the course of the study and PSA

progression assessment according to PCWG2 criteria

- Concomitant medications listing: update listing of all prescriptive and non-prescriptive (over the counter) medications taken since screening. This also includes any nutritional supplements and/or herbal preparations.
- Adverse events
 - AE follow-up to determine if any new or ongoing drug-related AE or any SAE regardless of relationship to study drug exists is required for 30 days post last dose or until patient receives anticancer therapy, whichever comes first
- Final dosing compliance check if not performed when treatment discontinued.
- Pain (BFI-SF) and Analgesic Usage Score
- Research Biomarkers
 - Circulating CTC collection (if not obtained at treatment discontinuation)
 - Circulating plasma for DNA, RNA studies (if not obtained at treatment discontinuation)
 - Paxgene miRNA studies (if not obtained at treatment discontinuation)
 - Urine and plasma metabolomics (if not obtained at treatment discontinuation)
 - Urine markers of bone turnover and RNA (if not obtained at treatment discontinuation)
 - Serum proteomic studies (if not obtained at treatment discontinuation)

11.2.6 3 monthly follow up (3 monthly from EOT)

Following treatment completion, patients will be followed for survival. Additional information as to whether they have started any platinum-based chemotherapy, mitoxantrone or another PARP inhibitor will be obtained where feasible. Follow-up data may be collected by a telephone interview.

11.3 Unscheduled Visits

Unscheduled visits and procedures may be conducted at the investigator's discretion for the safety follow-up of the patient. Such visits and procedures must be fully recorded in source documents regarding the purpose and outcome of the visit/assessment. Clinically significant laboratory results from unscheduled visits should be documented in the eCRF.

11.4 Early Discontinuation

Patients will be advised in the written informed consent form that they have the right to withdraw from study drug treatment at any time without prejudice, or may be withdrawn at any time at the discretion of the investigator or the sponsor. Notification of early patient discontinuation from the study and the reason for discontinuation will be made on the protocol deviation form provided. Patients removed from therapy for any reason should continue to be followed for the collection of safety data as outlined in the EOT visit procedures. For patients who refuse or are unable to attend further clinic study visits, telephone contact should be attempted to follow up for adverse events 30 days +/- 5 days after the last dose of study drug. All serious adverse events will be followed until resolution,

until the event has stabilised and/or become chronic, until it has been determined that the event was caused by aetiology other than the study drug, or through 30 days, whichever comes first. Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete study-related assessments and retrieve any outstanding data and study drug. Such efforts should be documented in the source documents.

Table 2: Schedule of Procedures and Clinic Visits

Procedures & Assessments	Screening		Cycle 1	Cycle 1	Cycle 1	Cycle 2, 3, 5, 6, 8, 9, 11, 12	Cycle 4, 7, 10, every 3 rd cycle	Cycle 4, 7, 10, and every 3 rd cycle	End of Treatment (EOT) Visit	Follow Up
	Day -28 to Day -1	Day -14 to Day -1	Day 1	Day 8	Day 15	Day 1	Up to 8 days before	Day 1	Day 30 after last dose of drug	3 monthly from EOT
Informed Consent ¹	X									
Medical History ²		X								
Obtain Archival Tissue ³	X									
Tumour Biopsy ⁴	X			X(8± 21 days)					X (optional)	
Assessment of Symptoms ⁵		X	X	X		X		X	X	
Dosing compliance ⁵				X		X(every cycle)		X		
Concomitant medication ⁵		X	X	X		X		X	X	
Adverse events ⁵			X	X		X		X	X	
Physical Examination & Vitals ⁶		X	X		X	X		X	X	
Complete Pain Questionnaire ⁷		X	X			X(every cycle)		X(every cycle)	X	
12 Lead ECG ⁸		X								
Safety Bloods ⁹		X	X	X		X		X	X	
Testosterone Level ¹⁰		X								
PSA Levels ¹¹		X	X					X	X	
Imaging Assessments										
Bone Scan ¹²	X						X			
DW-MRI (optional) ¹³	X						X			
CT Scan ¹⁴	X						X			
Disease Progression Assessment ¹⁵	X							X	X	
Survival & further treatment										X
Biomarker Tests (patients should be fasted for at least 8 hours prior to blood draw – see 14.3)										
Buccal Swab ¹⁶		X								
Saliva ¹⁷		X								
Plasma DNA & RNA ¹⁸		X	X	X		X (C2,3,5)			X	
Circulating Tumour Cells ¹⁹	X		X	X	X	X (C2, 3)		X	X	
Blood miRNA ²⁰		X	X			X (C3,5)			X	
Plasma Proteomics ²¹		X	X						X	
Plasma and urine Metabolomics ²²		X	X	X		X (C2,3,6)			X	
Markers of Bone Turnover and RNA ²³	X		X			X(C3,6)			X	

Procedures and Clinic Visits

1. Written informed consent must be obtained within 28 days period prior to Cycle 1 Day 1.
2. Medical history at screening will detail demographic, family history, co-morbidities, prior treatments for prostate cancer and baseline adverse events.
3. Archival tumour tissue will be obtained for molecular characterisation. Patients who do not have archival tumour tissue will be required to have a repeat tumour biopsy in order to obtain the required tumour tissue for histological confirmation and for subsequent molecular characterisation.
4. Fresh tumour biopsies are a mandatory component of this study and will be obtained prior to commencing treatment (during the screening period) and post treatment (at any point from Day 8 to Day 28 of Cycle 1). The third biopsy at the time of treatment discontinuation is optional.
5. At each clinic review, symptoms, concomitant medication, treatment compliance and adverse events will be assessed. Adverse events will be assigned a grade according to the CTCAE version 4.02 and causality. Adverse Event follow-up is required for 30 +/-5 days post last dose of treatment to determine if any new or on-going drug related AE or any SAE regardless of relationship to drug persists.
6. Includes physical examination, blood pressure, heart rate, respiratory rate, oral body temperature, and weight. Height will only be measured at the screening visit. A full physical examination will be performed at screening, Cycle 1 Day 1 and at the EOT visit. At all other clinic reviews physical examinations will be performed as clinically indicated.
7. A Brief Pain Inventory Questionnaire will be given to the patient to fill in at screening and at the beginning of each cycle. The Brief Pain Inventory Score will be annotated in the patients CRF.
8. ECG will only be performed at the screening visit. ECGs should be obtained with the subject in the supine resting position for several minutes. Abnormal ECG related to electrolyte abnormalities should be repeated following the correction of the electrolyte abnormalities. ECGs will only be repeated beyond screening if clinically indicated.
9. A full array of safety bloods including the full blood count, blood chemistry, liver function test, clotting profile, glucose, amylase, etc. will be obtained and checked at the beginning of each cycle of treatment.
10. Serum testosterone level will be checked during the screening period to ensure a systemically castrate state [testosterone levels of < 50 ng/dL (< 2.0 nM)]. Testing for serum testosterone, PSA and routine safety bloods will be performed at the local site laboratory.
11. PSA testing will be done at screening and every 12 weeks while on treatment. PSA responses by PCWG2 criteria will need to be confirmed 4 or more weeks later.
12. A bone scan will be obtained at baseline and after every 3rd cycle of treatment. New bone deposits will need to be confirmed with a repeat bone scan 6 or more weeks later.
13. DW-MRI is optional and will be performed at baseline (screening) and every 12 weeks thereafter.
14. CT scan will be obtained at baseline and after every 3 cycles of treatment. If a status of partial or complete response is made, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.
15. Disease progress assessment will be made after every 3rd cycle of treatment at the clinic visits.
16. A buccal swab for DNA analysis should be collected at the indicated time point
17. Saliva for DNA analysis should be collected using an Orangen Kit at the indicated time point
18. Serum plasma for circulating plasma DNA and RNA will be collected at the indicated time points in BD Vacutainer® CPT™ tubes (3x10mls).
19. Blood for CTC analysis should be collected at the indicated time points in 2 Cell Save™ tubes (10mL each, Veridex, PA).
20. Blood samples for whole blood miRNA analysis will be collected at the indicated time points in a 2.5ml PAXgene Blood RNA Tube
21. Blood samples (1x8.5mls) will be collected for PTEN proteomics profiling at the indicated time points.
22. Urine and plasma metabolomics profiles will be evaluated both at baseline and during treatment at the indicated time points. Blood samples (2x6mls) will be collected in a 6ml BD vacutainer with heparin -5min pre dose and 2 hour post dose. A 24 hour urine collection will be collected.
23. Urine collected after the void of the first morning sample will be collected at the indicated timepoints to assess markers of bone turnover such as telopeptides.

Patients should be fasted for 8 hours prior to all blood samples on the days where metabolomic samples are collected (screening, C1D1, C1D8, C2D1, C3D1, C6D1 and EOT).

12 TRIAL TREATMENT

12.1 Drug Manufacturer

Olaparib tablets will be manufactured and provided free of charge by AstraZeneca to participating centres. AstraZeneca will manufacture to Good Manufacturing Practice (GMP) and UK Legislation.

12.2 Presentation / Formulation of Olaparib

Olaparib is presented for oral administration as a green, oval bi-convex film-coated tablet containing 100 mg of drug substance.

12.3 Drug, Dose and Schedule

The dose of 400 mg olaparib, twice daily orally, continuous dosing has been selected for this protocol based on the pharmacokinetic (PK), pharmacodynamic (PD) and clinical efficacy data from the Phase I-II studies including an ongoing bioavailability study (10, 11, 49, 50, 61, 62). The olaparib dose should NOT be adjusted according to the patient's body weight, even for very heavy or light patients. Patients will be given sufficient supplies for 1 cycle (28 days) of treatment. If a patient is not able to attend the clinic review due to a public holiday falling on the 28th day of the cycle or for other unforeseen circumstances consideration should be given to ensure the patient has sufficient drug supplies

Patients should be advised to withhold study drug on the morning of their clinic appointments for trial assessments.

12.4 Instructions for Administration of Olaparib

Patients should swallow the olaparib tablets whole with a glass of water in the morning and evening at the same times each day to ensure a dose interval of approximately 12 hours. All doses should be taken with approximately 240mL of water (1 glass of water) and can be taken with a light meal. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. If vomiting occurs shortly after the olaparib is swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the trial miss a scheduled dose for whatever reason (e.g. as a result of forgetting to take the dose of olaparib), he will be allowed to take the scheduled dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

12.5 Olaparib Treatment Compliance

A member of the Investigative site's study team will query the patient for treatment compliance at day 1 of each new cycle of treatment. All patients must return their bottles of

olaparib at the appropriate scheduled visit, when new bottles will be dispensed. Compliance will be assessed by capsule count and questioning by the study nurse and the information will be recorded.

12.6 Duration of Therapy

Patients may continue with olaparib treatment as long as they remain free from intolerable toxicity, in the Investigator's opinion, are receiving clinical benefit and do not meet any discontinuation criteria (see Section 10.9 for discontinuation criteria).

12.7 Supportive Care Guidelines

Based upon experience from Phase I and II studies, olaparib is generally well tolerated. The safety concerns are primarily related to the risk of myelosuppression. Supportive care should be provided therapeutically and prophylactically as deemed necessary by the treating physician including but not limited to the items outlined below:

Gastrointestinal symptoms

Prophylactic anti-emetics and/or anti-diarrhoeals will not routinely be given. Should a patient develop nausea, vomiting and/or diarrhoea that, in the Investigator's opinion, is considered to be related to olaparib, then appropriate prophylactic treatment may be initiated. Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

Myelosuppression

Routine prophylaxis with granulocyte colony-stimulating factor (G-CSF)/granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin is not recommended. Nevertheless, use is permitted at the Investigator's discretion and according to local hospital guidelines. The occurrence of leukopenia and/or anaemia should be managed as deemed appropriate by the investigator. The use growth factors must be discontinued once the AE has recovered to CTCAE grade 1 or better. They may be resumed, if necessary, if leukopenia/anaemia develops again and discontinued once it recovers. The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the eCRF. Checking haematinics levels (Iron, B12 and folate) and providing supplementation if these are found to be low is advocated. Transfusions may be given as clinically indicated for the treatment of anaemia and thrombocytopenia.

Symptoms Related to Castration

Treatment with androgens, estrogens and progestin to control hot flashes is not allowed. Antidepressants that do not interfere with P450 enzyme function are permitted for the management of hot flashes. Long-term androgen deprivation may lead to metabolic diseases, such as glucose intolerance, hypercholesterolemia, and osteoporosis,

appropriate medication may be prescribed to manage these conditions. All such AEs need to be recorded.

12.8 Guidelines for Management of Toxicity and Dose- Modification

Based on Phase I and Phase II studies, olaparib is generally well tolerated. Safety concerns are mainly related to the possibility of myelosuppression.

Any toxicity observed during the course of the study may be managed by a dose interruption if deemed appropriate by the Investigator. Treatment must be interrupted if any clinically significant NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of olaparib.

Repeat dose interruptions are allowed as required, for a maximum of 42 days on each occasion. Olaparib must be interrupted until the patient recovers completely or the toxicity reverts to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.02) grade 1 or less. When the toxicity is appropriately resolved, the patient can resume treatment with olaparib with a dose reduction according to Table 3 if a treatment break of ≥ 14 days was required for the resolution of the toxicity. If the event recurs with the same severity following olaparib re-challenge, treatment should be interrupted again, and on resolution, a further dose reduction made. A maximum of 3 dose reductions will be allowed. Regular 7-day drug holidays will also be permitted if myelosuppression is an issue at these doses.

If, on re-starting treatment following 3 dose reductions, the event continues to occur at the same severity, treatment should be discontinued and the patient withdrawn from study. If the toxicity has not resolved to at least grade 1 during the maximum 42-day period, and/or the patient has already undergone a maximum of 3 dose reductions already, the patient must permanently discontinue treatment with olaparib. Once the dose of olaparib has been reduced under no account should it be re-escalated.

The dose of olaparib should not be reduced for grade 3-4 gastrointestinal adverse events that have not been adequately managed with appropriate prophylactic measures. In all cases where the olaparib dose has been interrupted or the patient discontinued due to unusual or unusually severe toxicity considered related to olaparib, the Investigator must contact the Chief Investigator and CTSU trial management team. All dose modifications and interruptions (including any missed doses), and the reasons for the modifications/interruptions are to be recorded in the eCRF.

Olaparib should be temporarily withheld in the event of:

- Grade 4 neutropenia
- Grade 2-4 neutropenia with infection
- Platelet count lower than $50 \times 10^9/L$
- Non-haematological toxicity grade 3 or greater, except nausea, vomiting or diarrhoea and fatigue associated with suboptimal pre-medication and/or management OR transient and clinically insignificant biochemical blood results.

- Aspartate transaminase (AST) or alanine transaminase (ALT) elevations grade 3 or higher for more than 7 days.
- New or worsening pulmonary symptoms or radiological abnormality occurs which are suggestive of pneumonitis
- Any other toxicity that, in the view of the principal investigator and the medical monitor, represents a clinically significant hazard to the patient until resolution of toxicity to no more than grade 1.

Standard Dose	Olaparib Dose
First dose reduction due to NCI-CTC grade 3 or 4 treatment-related Serious Adverse Events / Adverse Events (excluding inadequately managed gastrointestinal symptoms)	300 mg BID
Recurrent episode of NCI-CTC grade 3 or 4 event despite one previous dose reduction (excluding inadequately managed gastrointestinal symptoms)	200 mg BID
Recurrent episode of NCI-CTC grade 3 or 4 event despite two previous dose reductions(excluding inadequately managed gastrointestinal symptoms)	100mg BID

Table 3: Summary Guidelines for Dose Reductions

Management of prolonged haematological toxicities including anaemia, neutropenia or thrombocytopenia whilst on study treatment

If any study treatment is interrupted/ delayed because of one or more of the following:

- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 neutropenia
- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 thrombocytopenia
- ≥ 2 week interruption/delay in study treatment due to CTC grade >2 anaemia and or development of blood transfusion dependence

Weekly blood counts should be performed during the study treatment interruption/delay. If the levels have still not recovered to CTC Grade ≤ 1 after 42 days of dose interruption, the patient should be referred to a haematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Bone Marrow or blood cytogenetic analysis:

If a bone marrow analysis is carried out to evaluate cytopenia it should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Development of myelodysplastic syndrome should be reported as an SAE and full reports must be provided.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Chief Investigator and CTSU trial management team. All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded.

12.9 Packaging and Labelling

AstraZeneca have employed Fisher Clinical Services to coordinate IMP packaging, labelling and distribution for this trial. Olaparib will be supplied in High Density Polyethylene containers containing desiccant. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence. Olaparib will be provided to each site in labelled bottles. Each bottle will have a label permanently affixed to the outside and will be labelled in accordance with Good Manufacturing Practice and local regulations, stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. Labels will refer to Olaparib as AZD2281 and will include blank lines for quantity of tablets to be taken, patient trial ID and date of dispensing.

12.10 Drug Storage

Drug Storage by Pharmacy

All study medication must be kept in a secure place under appropriate storage conditions (at temperatures less than 30°C and protected from light). Study medication should not be stored under refrigerated conditions. Additional information is provided in the olaparib Investigator's Brochure. Any deviations from the recommended storage conditions should be immediately reported to the sponsor and the use of olaparib interrupted until authorisation for its continued use has been given by AstraZeneca and the sponsor.

Storage Requirements for the Patient

Olaparib must be stored in the bottle with the cap tightly on at room temperature. Study medication should not be refrigerated. Patients should be advised to keep all medication out of the sight and reach of young children.

12.11 Distribution of Drugs to Site

No drug will be distributed to participating centres unless ICR-CTSU is satisfied that the required approvals, agreements and initiation procedures are complete.

Participating pharmacy departments should contact Fisher Clinical Services via the ICR-CTSU trial management team to request drug supplies following patient registration.

Records must be kept for all deliveries and a copy of the order / delivery note placed in the Site Pharmacy File and kept within the pharmacy department as in routine practice. At the end of the trial, it must be possible to reconcile supply and usage of all stock. Account must be given to any discrepancies and certificates of delivery and return must be signed.

12.12 Pharmacy Responsibilities and Drug Accountability

Labelling:

Labelling will be the responsibility of Fisher Clinical Services and will be compliant with Annex 13 of the Good Manufacturing Guidelines (GMP) and all applicable local regulatory requirement. Each hospital pharmacist must also insert the name of the Principal Investigator (PI) or hospital specific code by which the PI can be identified, together with the Trial ID and patient's name,.

The local pharmacy department must designate a responsible person for ensuring that:

- The study drug is handled and stored safely and properly
- The study drug is labelled for each patient in accordance with Annex 13 of the EU Good Manufacturing Practice (GMP) Guidelines
- The study drug is dispensed only to trial patients and in accordance with the protocol and under the guidelines of the site's dispensing standard operating procedure
- Full accountability is maintained for the study drug
- Patients should be instructed to return unused olaparib, preferably in their original packs. Olaparib which has been dispensed to a patient and returned unused must not be re dispensed to a different patient
- There is a sufficient supply of study drug for patients' continued treatment, and in a timely manner, contact ICR-CTSU for re-supply of stock
- Study drug expiry dates are monitored and are used in order of expiry date order i.e. earliest expiry first
- All unused drugs will be accounted for and retained until advised otherwise. Unused and returned study drug may be destroyed locally in accordance with hospital protocol and following written instructions from the sponsor

Patient cards

Small wallet sized cards will be produced by ICR-CTSU on request by the participating centre. Each card will state:

- the name of the participating centre
- that the patient is participating in the TOPARP trial
- that the patient is taking olaparib

12.13 Concurrent Medications

The concurrent administration of other anticancer therapies, including cytotoxic, hormonal (except LHRH analogues) or immunotherapy, is prohibited during study treatment. The use of any natural/herbal products or other “folk remedies” should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded.

Olaparib is an investigational drug for which no data on *in vivo* interactions are currently available. Based on *in vitro* data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. *In vitro* data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib. Whilst this is not an exhaustive list of inhibitors, it covers the known potent inhibitors which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfonavir

For patients taking any of the above, the required wash-out periods prior to starting olaparib is one week.

In addition, to avoid potential reductions in exposure due to drug interactions, the exclusion of the following P450 inducers is recommended:

- Phenytoin, rifampicin, rifapentin, reifabutin, carbamazepine and phenobarbitone, nevirapine, modafinil and St John’s Wort (*Hypericum perforatum*)
- For patients taking any of the above, the required wash-out periods prior to commencing olaparib are:
- Phenobarbitone - 5 weeks; any of the others - 3 weeks.

If use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient’s safety and welfare, the Investigator must contact the ICR-CTSU and a decision to

allow the patient to be enrolled in the study will be made on a case-by-case basis by the Chief Investigator.

If at any time an investigator suspects a drug-drug interaction due to olaparib, an AE report should be completed and the study sponsor informed.

Permitted Concomitant Therapy

- Leuteinizing hormone-releasing hormone (LHRH) agonists to maintain a testosterone level <50g/dL should be administered in patients who have not undergone an orchidectomy.
- Conventional multi-vitamins and minerals.
- Stable chronic non-immunosuppressive systemic doses of corticosteroids up to a dose of prednisolone 5mg BID or equivalent so long as the treatment was initiated prior to commencing the trial medication with evidence of progression on the dose of steroids. Higher doses of steroids are permitted if clinically indicated for acute medical conditions.
- Initiating bisphosphonate therapy or adjusting bisphosphonate dose/regimen within 30 days prior to Cycle 1 Day 1 is prohibited. Patients on a stable bisphosphonate regimen are eligible and may continue.
- Anticoagulant Therapy: Patients who are taking warfarin may participate in this trial however, it is recommended that prothrombin time (International Normalised Ratio [INR] and activated partial thromboplastin time [APTT]) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted and is preferable given the potential for myelosuppression.
- **Palliative radiotherapy:** may be used for treatment of pain at the site of bony metastases that were present at baseline, providing the Investigator does not feel that this is an indication for the patient to come off treatment due to disease progression. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the eCRF.

Therapy considered necessary for the subject's welfare and which is believed not to interfere with the study medication may be given at the discretion of the investigator. If concurrent medications may have an effect on study outcomes, a statement to the effect that these medications should be administered in dosages that remain constant throughout the course of the trial should be included. All medications (prescriptions or over-the-counter medications), the reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records.

13 PHARMACOVIGILANCE

13.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a study drug, whether or not considered related to the study drug.

Adverse Reaction (AR): all untoward and unintended responses to the study drug related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions i.e. an AR is possibly, probably or definitely related to the study drug. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR): Any untoward medical occurrence or effect which occurs from screening until 30 days after the last dose of study drug:

- **results in death:** the patient's death is suspected as being a direct outcome of the AE.
- **is life-threatening:** refers to an event in which the subject was at risk of death at the time of the event. It also refers to an event that would result in death with the continued use of the product; it does not refer to an event which hypothetically might have caused death if it were more severe.
- **requires hospitalisation, or prolongation of existing inpatient hospitalisation:** admission to hospital overnight or prolongation of a stay in hospital was necessary as a result of the AE..
- **results in persistent or significant disability or incapacity:** the AE results in a significant or persistent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- **results in a congenital anomaly or birth defect**

Hospitalisation meeting the definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Inpatient admission does not include: rehabilitation facilities, hospice facilities, skilled nursing facilities, nursing homes, routine emergency room admissions, same day surgeries (as outpatient/same day/ambulatory procedures), or social admission (e.g., subject has no place to sleep). Outpatient treatment in an emergency room is not itself an SAE, although the reasons for it may be. Hospital admissions/surgical procedures planned for a pre-existing condition before a patient is randomised to the study are not considered SAEs, unless the illness/disease deteriorates in an unexpected way during the study

Medical judgement should be exercised in deciding whether other AE/ARs are serious. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious

N.B. progressive disease and death due to disease are not considered SAEs but should be reported on the relevant forms.

Suspected Unexpected Serious Adverse Reaction (SUSAR): Any serious adverse event with a suspected relationship to study drug that is not listed on the Investigator Brochure (IB) and in the opinion of the Chief Investigator, is unexpected.

13.2 Clinical & Laboratory Adverse Events

AEs Based on Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

AEs Based on Examinations & Laboratory Tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfil any of the SAE criteria or are the reason for stopping treatment with the investigational product. If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator should use the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value).

The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms.
- Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting as an AE).
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy.
- Test result leads to any of the outcomes included in the definition of a SAE.
- Test result is considered to be an adverse event by the investigator or sponsor.

- Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for bullet point 4.
- Relevant clinically significant laboratory results should be recorded in the patient's eCRF.

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the sponsor (or his/her designated representative), or until a diagnosis that explains them is made.

13.3 Causality

Many adverse events that occur in this trial, whether they are serious or not, will be known treatment related toxicities. The Principal Investigator is responsible for the assessment of causality of serious adverse events (see definitions of causality table).

If there is any doubt about the causality of an event, the investigator should inform ICR-CTSU who will notify the Chief Investigator. The drug manufacturer and/or other clinicians may also be asked for advice.

13.4 Severity of Adverse and Serious Adverse Events

Adverse event (AE) severity is a clinical determination of the intensity of an AE and SAEs. The severity assessment for a clinical AE should be completed using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.02). Any AE not listed in the CTCAE will be graded as follows:

Table 4: Severity of Event

Grade	Definition	Description
1	Mild adverse event	Does not interfere with the patient's usual function [awareness of symptoms or signs, but easily tolerated (acceptable)].
2	Moderate adverse event	Interferes to some extent with the patient's usual function [enough discomfort to interfere with the usual activity (disturbing)].
3	Severe and undesirable adverse event	Interferes significantly with the patient's usual function [incapacity to work or to do usual activities (unacceptable)].
4	Life-threatening or disabling adverse event	Results in risk of death, organ damage or permanent disability (unacceptable).

5	Death related to adverse event. Relationship to Study Drug	Event has a fatal outcome.
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Causality of Event

A determination should be made by the investigator regarding the relationship (if any) between an AE and the study drug. A causal relationship is present if there is a reasonable possibility that the AE may have been caused by the study drug. The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study.

Table 5: Definitions for Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

The expectedness of a SAR related to the study drug should be assessed by the Chief Investigator in accordance with the information provided in the IB for olaparib.

Expected SARs should be reported as per the SAE reporting guidelines. SAEs should be reported up to 30 days after the patient's last dose of study medication

A summary of 'expected' adverse reactions as stated in the IB is listed below:

Table 6: Expected Adverse Reactions (Olaparib Monotherapy)

Frequency of Adverse Events	Very common	Common	Rare
Grade (G)	Mild to moderate	Mild to moderate	Mild to moderate
	CTCAE:G1-2	CTCAE:G1-2	CTCAE:G1-2

Adverse Events	Nausea	Anaemia	Lymphopenia
	Vomiting	Headache	Tachycardia
	Fatigue	Dyspepsia	Thrombocytopenia
		Dizziness	Neutropenia
		Asthenia	
		Decreased appetite	
		Dysgeusia	
		Constipation	

13.5 Procedures for Recording and Reporting Adverse Events

13.5.1 Reporting Serious Adverse Events (SAEs) to ICR-CTSUS

Any SAE that occurs from the time of screening and up to 30 days following the last dose of olaparib must be reported, whether or not considered causally related to the study treatment. For patients that do not enter the trial SAEs should be reported from screening until a decision is made the patient will not enter the trial. Any SAEs reported in this period should be followed until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised

All SAEs should be reported to ICR-CTSUS, within 24 hours of the study team becoming aware of the event, by completing the trial specific SAE forms and faxing to:

The ICR-CTSUS safety desk
Fax no: 0208 722 4368
For the attention of the TOPARP Trial team

Investigators or other site personnel must ensure that:

- All SAE forms must be completed, signed and dated by the Principal Investigator or designated representative.
- All SAE reports are supported by documentation in the patient's medical records. Obtain and maintain in his files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
- All patients with a serious adverse event must be followed up and the outcomes reported in a follow up severe adverse event report form to the ICR CTSUS.
- In the event of fatal or life-threatening AEs where important or relevant information is missing, active follow-up must undertaken immediately.

13.6 Review of Serious Adverse Events (SAEs) or Reactions (SARs)

Reported events / reactions using the SAE forms will be assessed by the Chief Investigator (or designated representative) for causality and expectedness.

NB. The Chief Investigator cannot down grade the Principal Investigator's assessment of causality.

SAEs assessed as having a causal relationship to study drug and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities by ICR-CTSU (see figure 4 for SAE reporting).

Centres should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of the SAE.

13.7 Expedited Reporting of SUSARs

If an SAE is identified as being a SUSAR by the Chief Investigator, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Main REC, the sponsor institutions and AstraZeneca within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the Chief Investigator, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Main REC, the sponsor institutions and AstraZeneca within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA, Main REC, the sponsor institutions and AstraZeneca as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

The Principal Investigators at all actively recruiting centres will be informed of any SUSARs occurring within the trial at regular intervals.

13.8 Follow up of Serious Adverse Events

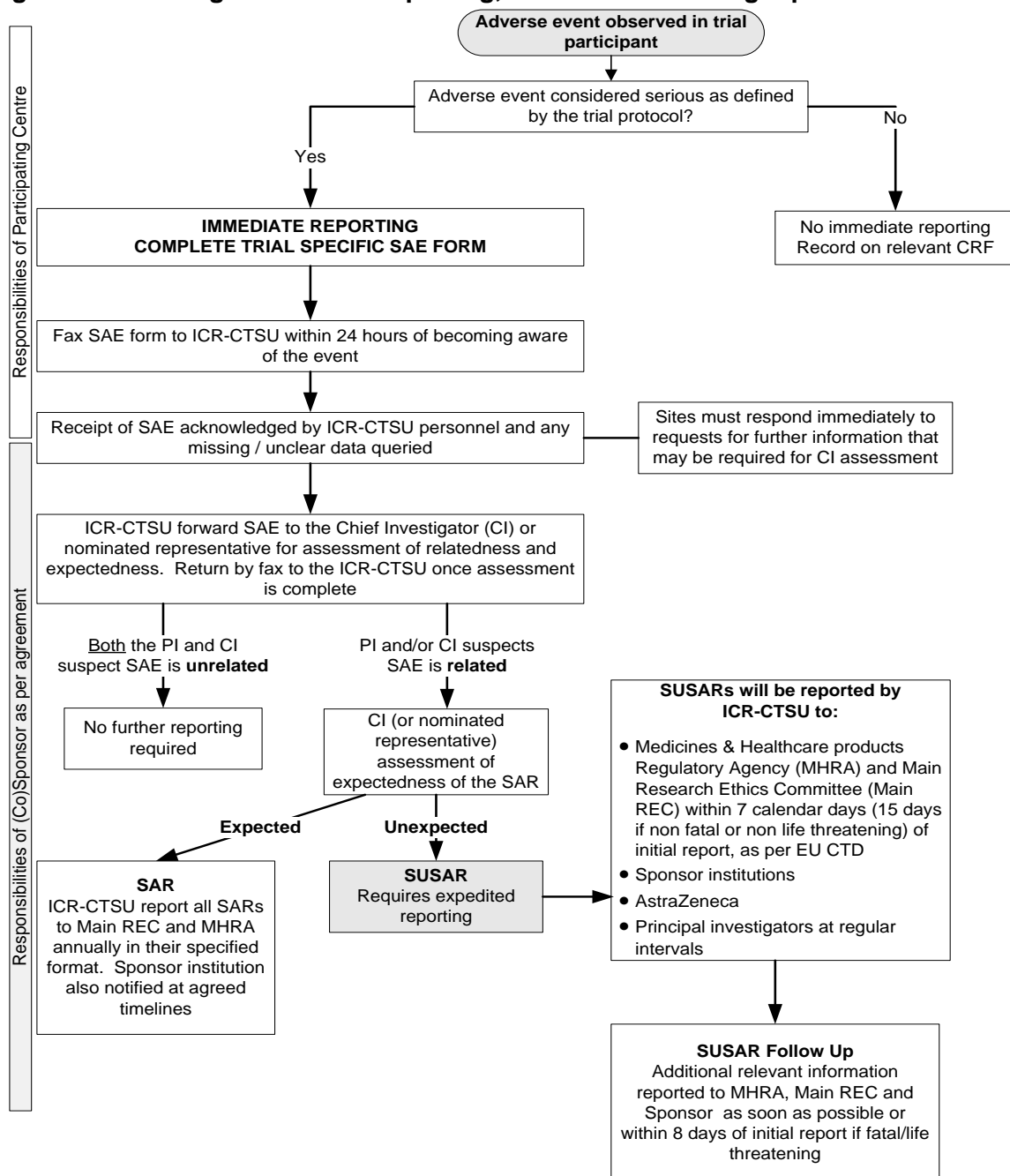
Centres should continue to follow up SAEs until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Information on outcome of the SAE should be completed on the relevant part of the original SAE and faxed to ICR-CTSU as soon as the Principal Investigator becomes aware.

NB Any male patient who fathers a child whilst on study medication must be followed up and the outcome reported to ICR-CTSU who will then forward the details to AstraZeneca.

13.9 Annual Reporting of Serious Adverse Reactions

An annual report will be provided to the MHRA and the Main REC, by ICR-CTSU and copied to the Co-sponsors, on the anniversary of the date when the Clinical Trials Authorisation (CTA) was obtained. This will include all related events reported on SAE forms, and a report from the Independent Data Monitoring Committee (IDMC).

Figure 4: Flow diagram for SAE reporting, and action following report



NB. All SAE's should continue to be followed up as specified in the protocol.

14 STATISTICAL CONSIDERATIONS

14.1 Trial Design

The aim of this design is to look for potentially sensitive subgroups of patients by undertaking a screening trial (part A) followed by a validation trial (part B) if there is evidence a sensitive subgroup exists.

Both of these trials are non-randomised with response rate being assessed at 6 months post registration as the primary endpoint. These trials will be followed by a randomised phase II trial (part C) in the sensitive patient groups with overall survival as the primary endpoint. The aim is to identify a sensitive subgroup with a 50% response rate on the basis that high response rates are necessary to be confident of demonstrating a survival benefit, the primary goal of the phase II strategy.

It is possible that all patients are sensitive to treatment in which case it has to be possible to apply the same efficacy and inefficacy criteria as are used in the validation trial to all patients in the screening trial.

Part A

The screening trial will involve all comers (unselected patients) and is an open-labelled, multi-centre two-stage design based on $H_0: p_0=0.05$; $H_a: p_1=0.20$; $\alpha=0.02$ and $\beta=0.10$. It will recruit a **maximum of 45 patients** (30 in stage 1 and 15 in stage 2) with an initial efficacy level of 20% and an inefficacy level of 5%, to allow for the fact that only a small subset of patients may be sensitive to olaparib.

This part will evaluate the anti-tumour activity of olaparib in unselected CRPC patients and will identify potential biomarkers of response.

- **Stage 1**

The first stage will enrol 30 patients and when all 30 have been followed up for a minimum of 6 months an interim analysis will take place to evaluate the response rate:

Given the efficacy level of 20% and inefficacy level of 5% the trial will be terminated with the conclusion of inefficacy if there are **2 or fewer responses**. If there are **15 or more responses** in the first stage, broad efficacy will be concluded and no more patients will be entered and Part C will commence in unselected patients.

If between **3 to 14 patients respond**, patient accrual will continue to a total of 45 patients (stage 2) and an investigation into the identification of a potential biomarker of response will be carried out.

- **Stage 2**

If the trial progresses to stage 2, a further 15 patients will be recruited, giving a total of 45 patients for part A. An interim analysis will be triggered once 45 patients have been followed up for a minimum of 6 months or alternatively we observe 23 or more responses. The recruitment will be halted.

If **23 or more** patients respond, Part C will be initiated. If **5 or fewer patients** respond, the null hypothesis will be accepted and the study will be terminated. If **between 6 and 22 patients respond**, an investigation into the identification of potential biomarkers of response will be carried out. If a potential biomarker subgroup is found, Part B will be undertaken. If a subgroup is not found, then Part C will be undertaken if at least 19 of the patients have responded, otherwise the study will be terminated since sufficient activity has not been observed based on $H_0: p_0=0.3$; $H_a: p_1=0.5$; $\alpha=0.059$ and $\beta=0.11$.

Deriving a classifier for identification of tumours with high susceptibility to PARPi olaparib in CRPC.

All patients participating in this trial will have their archival tissue, fresh tumour biopsies and circulating tumour cells collected prior to starting olaparib. The primary biomarkers to be evaluated include PTEN loss by IHC and FISH, *ETS* gene rearrangements by FISH and RAD51 foci formation. It should be noted that PTEN loss and *ETS* rearrangements co-associate and are found in approximately 50% of prostate cancers. In addition that is emerging evidence to suggest that RAD51 foci formation is diminished in tumours with HR defects such as those with loss of PTEN and *ETS* rearrangements (15, 27, 41, 44).

See section 2.1 for a discussion of relevant biomarkers.

Biomarkers will be classified as either established markers of sensitivity to synthetic lethality with PARPi (e.g. *BRAC1* -/-, *BRAC2* -/-), or as exploratory biomarkers. Established biomarkers will have a guaranteed place in the biomarker classifier but exploratory biomarkers will have to be shown to have predictive ability from the trial data.

The correlation between biomarkers will first be examined using Spearman's rank correlation. If two biomarkers are highly correlated or known to be highly correlated from previous evidence one of the biomarkers will be dropped. The use of appropriate cut-points of continuous scores for individual biomarkers will be decided before examining their association with response.

For potential promotion to the classifier, a false discovery rate of 10% or less will be applied to all exploratory biomarkers, using the p-values from the univariate association with response (Fisher's exact test, $p < 0.10$ 2-sided). If evidence exists from other sources it may be incorporated into the assessment of specific biomarkers using meta-analysis to give an 'overall' p-value.

Secondly, identification of a multivariable predictive classifier will be undertaken using a significance level of 10% or less for the inclusion of the biomarker in the classifier (logistic

regression). In the event of a tie, e.g. two or more classifiers with similar performance, a liberal approach will be adopted on the basis that it will be possible to exclude non-responsive biomarker groups at a later date. Standard prognostic factors may be included in the classifier if they are independent of the biomarkers.

The goal will be to develop a classifier which identifies a group with a response rate of 40% or more on the basis that the levels for inefficacy and efficacy are set at 30% and 50% respectively.

The biomarker defined subgroup satisfying the above criteria will be selected for validation in Part B. If olaparib successfully graduates from this, stage Part C will be undertaken. If convincing evidence arises from other translational studies of olaparib or other PARP inhibitors the IDMC will be asked to advise whether or not an analysis should take place.

Part B

The biomarker status of patients registered in Part B will be evaluated and only patients with the presence of the putative biomarker subgroup identified in Part A will be entered. Forty-four additional patients will be treated in this single stage, which assumes $H_0: p_0=0.3$; H_a ; $p_1=0.5$; $\alpha=0.05$ and $\beta=0.15$.

If **19 or more** of the **44 patients** respond (43%), then a proposal for a subsequent randomised controlled trial to investigate the predictive potential of the biomarker will be developed. If **18 or less** patients respond, the study will be terminated.

Further information regarding the sample size calculations of both parts A and B is shown in Appendix A. The detectable effects in the biomarker sensitive group assuming 80% power are presented on Appendix B.

14.2 Analysis populations

Analysis populations are defined as follows:

- **Intention to treat (ITT):** This population includes all patients enrolled into the study regardless of whether they are later found to be ineligible, a protocol violator, never treated or not evaluated. Patients for whom the primary endpoint cannot be evaluated will be treated as non-responders.
- **Evaluable-patient population:** This population contains all enrolled patients for whom the primary endpoint can be evaluated. A patient will be “evaluable” if **at least a bone scan or RECIST measurement is available. Where evaluability is difficult to define the final decision will rest with the IDMC.**
- **Per protocol (PP):** This population contains all enrolled patients who received at least 1 cycle of olaparib without major protocol violations.
- **Safety population:** This population includes all enrolled patients who received at least 1 dose of olaparib.

The analysis of the primary outcome will use the evaluable-patient population with sensitivity analyses in the ITT and per protocol populations. All other analyses will use the ITT

population. The ITT and PP analyses will treat non-evaluable patients as non-responders. The safety population will be used to further characterise the safety profile of olaparib in advanced CRPC patients.

14.3 Primary Efficacy Endpoint

Response will be defined by:

- Objective response by modified RECIST (baseline lymph node size must be ≥ 2 cm to be considered a target lesion) (Appendix E) and / or
- Conversion of circulating tumour cell count (CTC) to $< 5/7.5$ ml blood nadir confirmed by a second consecutive value obtained four or more weeks later and / or
- PSA decline of $\geq 50\%$ (according to the PCWG2) (Appendix D)

Failure will be defined as:

- Progression by RECIST- increase in measurable lesion size(S) or new lesion AND/OR
- Progression by bone scan – see Appendix D

Response will be evaluated 6 months post registration. The last value of PSA, CTC count, CT scan and bone scan on or up to four weeks before the date of first study treatment will be used as the baseline value for this assessment. The response rate will be presented along with its exact two-sided 95% confidence interval.

14.4 Secondary Efficacy Endpoints

The following endpoints will be assessed 6 months post registration. However, decisions made within the trial to comply with the adaptive design will not necessarily require 6 months follow up on all patients, e.g. it may be possible to enter patients into the second stage of Part A when it is clear between 3 and 14 responses will occur in the first stage even though not all 30 patients have 6 months follow up.

PSA response and PSA progression are defined according to the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA value from cycle 1 day 1 (baseline). This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. The first PSA reading will be obtained at week 12.

Time-to-PSA Progression

For patients who have achieved a $\geq 50\%$ decrease from the cycle 1 day1 (baseline), the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the **nadir** is documented. This must be confirmed by a second consecutive value obtained 4 or more weeks later. For patients without a PSA decrease of this magnitude or no decrease at all, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the **baseline** is documented. This must also be confirmed by a second consecutive value 4 or more weeks later. Time to PSA progression will be summarised using Kaplan-Meier methods.

Duration of PSA response

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the cycle 1 day 1 (baseline) value (must be confirmed by a second value) until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be assessed at the last PSA measurement. Duration of PSA response will be summarised by the median and presented along its 95% confidence interval.

PSA objective response rate (PSA-ORR)

The proportion of patients having achieved partial or complete response defined by PSA will be reported with the corresponding exact two-sided 95% confidence interval.

Pattern of PSA Responses

Waterfall plots will be presented (as per PCWG2 recommendations) that show the percentage of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy), as well as the maximum decline in PSA that occurs at any point after treatment. Waterfall plots provide a broader display of PSA changes than dichotomised responses.

CTC Response

The proportion of patients with a CTC conversion to $<5/7.5$ ml blood at nadir (confirmed by a second consecutive value obtained four or more weeks later) will be presented along an exact two-sided 95% confidence interval. Its association with PFS and OS will be examined via Cox regression models first univariately and subsequently in a multivariable model adjusting for potential confounders. Waterfall plots of CTC falls will also be presented that show the percentage change in CTC counts from baseline to 12 weeks as well as maximal CTC count declines that occur at any point after treatment.

The following endpoints will be evaluated using Kaplan and Meier methods:

Radiographic Progression Free Survival (rPFS)

Radiographic progression free survival (rPFS) will be defined by either RECIST progression and /or progression on bone scan (Appendix D and E). It will be measured from the date of trial entry to the first occurrence of radiographic progression or death from any cause. If no event exists, then rPFS will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Time to Radiographic Progression

Time to radiographic progression (progression defined by either RECIST progression and /or progression on bone scan) will be measured from the date of trial entry to the first occurrence of radiographic progression. Death from prostate cancer or any other cause without prior radiographic evidence of progression will not count as an event. If no event exists, then time to radiographic progression will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Progression Free Survival (PFS)

Progression free survival will be measured from the date of trial entry until radiographic progression, unequivocal clinical progression or death. If no event exists, then PFS will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Overall Survival (OS)

OS will be measured from the date of trial entry to the date of death (whatever the cause). Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow-up.

14.5 Tertiary/exploratory Endpoints

- **Pain palliation:**

Pain palliation will be assessed using the Brief Pain Inventory's (BPI Short Form) worst pain intensity score and average score. A composite of the four pain items (worst, least, average, right now) will be presented as supplemental information. Change in BPI score from baseline will be assessed at 6 months post registration. A reduction of two points in the worst pain score relates to an improvement of pain. The analgesic relief received will be described.

- **Safety Endpoint**

Safety analysis will be summarised using the safety population. Extent of exposure to study drug will be summarised and details will be provided. Treatment emergent adverse

events (AEs) are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose. Adverse events will be graded according to the NCI-CTCAE v4.02. Adverse events will be summarised by grade, according to the worst grade experienced. In addition, most frequently observed AEs will be summarised. In the summary of AE, an AE occurs more than once within a SOC and PT will be counted only once using the worst grade experienced. Serious AE and deaths observed within 30 days of the last dose of study treatment will be provided in a listing.

All adverse events resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of study drug will also be listed and tabulated by preferred term. Clinical laboratory test results will be collected pre-treatment and through 30 days post last dose of study treatment. All laboratory test results will be classified according to the NCI CTCAE v4.02 criteria. Standard reference ranges will be used for missing or discrepant normal ranges. Baseline laboratory test values are the results from the last blood samples drawn on or prior to the first day of study treatment. On-study laboratory test values are those results from blood samples drawn a day after the first study treatment up until 30 days after the last dose of study treatment.

- **Impact of treatment with olaparib on bone metastases imaging by DW-MRI.**

Diffusion-weighted MRI scan will be offered to patients recruited in part A and we expect approximately 50% acceptance rate. This analysis will be **purely exploratory** and we will examine whether response to olaparib expressed by changes in apparent diffusion coefficients produced by the DW-MRI scan correlate with 1) PSA decline, 2) CTC conversion and 3) radiological responses coming from conventional imaging. In 20 patients it is possible to detect a correlation coefficient of 0.6 which is equivalent to the parameter explaining 36% of the variation using a 2-sided 5% significance level.

14.6 Data Monitoring

An Independent Data Monitoring Committee will meet in confidence at regular intervals, firstly to review the safety analysis following the first 5 and 10 patients recruited and subsequently every 6 months (or at intervals determined by them) to review accrual, safety and efficacy data.

The replacement of patients who withdraw from the study or who are un-evaluable for reasons deemed not to be treatment related will be based on the advice of the committee. The committee will review the results of each interim analysis (progression from stage 1 to stage 2 and progression to part B) and will be asked to advise. For completeness a sensitivity analysis of the progression free rate calculated by the Kaplan Meier product limit method will also be presented in which withdrawals and deaths are censored. The summary statistic will be the progression free rate at 6 months together with its 95% one-sided confidence interval.

15 TRANSLATIONAL RESEARCH

Paraffin embedded tumour blocks or unstained sections from archival tumour tissue from the time of the original diagnosis or from a biopsy / resection of metastatic disease will be required from all subjects who enrol on the study. Patients who do not have adequate archival tumour tissue will be required to have tumour confirmed in a repeat tumour biopsy in order to be enrolled on the study. CTCs, urine, plasma samples and mandatory fresh tumour biopsies will be obtained at various time points during the study (Table 2 & 7). CTCs will be enumerated to evaluate conversion rates (CTC from ≥ 5 cells/7.5ml blood at baseline to < 5 cells/7.5mls) on this treatment. The tumour tissue will be assessed for multiple biomarkers including *PTEN* and *ERG* expression, *PTEN* deletions, *TMPRSS2-ETS* gene rearrangements using multicolour FISH studies, markers of DNA damage and HR repair such as γ H2AX and RAD51 focus formation, markers of tumour cell proliferation and cell cycle phase and mutational analysis through hotspot and/or whole genome sequencing. Blood samples for plasma-based biomarker will be utilised for several studies including obtaining normal germline DNA and circulating tumour DNA for mutational analysis (e.g. *BRCA1*, *BRCA2*, *CHEK2*, etc.), genome sequencing, quantitative real time polymerase chain reaction for *ERG* detection, proteomics, metabolomics, RNA and microRNA (miRNA) studies. Urine samples will be utilised to evaluate metabolomics, RNA and urine telopeptides profiles. Additional putative predictive biomarkers involved in the HR DNA repair pathway and sensitivity to PARP inhibition may be evaluated to facilitate the characterisation optimal determinants of response and resistance to olaparib treatment. Some of these additional markers/studies may come from other translational studies.

All the tumour tissue, CTC, plasma and urine samples will be sent to the Institute of Cancer Research Biomarker Group for processing and analysis. Some of these samples may be labelled with the patients' initials, hospital pathology number and trial number when they are sent to the research laboratory. When they arrive at the laboratory each sample will be coded with a unique anonymised number and any personal details removed. The number generated is linked to the patient trial ID held at the ICR CTSU. This coding system will maintain patient confidentiality whilst allowing biological details to be compared to treatment findings.

Samples will be stored in a secure area in the Cancer Biomarkers Laboratory at the Institute of Cancer Research. Samples will only be accessible by accredited staff involved in the processing and analysis of the samples. Some of the tumour/plasma samples collected may need to be sent to another site for processing and analysis. This will only occur following an established agreement being set up and assurance that patient confidentiality is maintained. **Instructions for the sample requirements, collection, handling, labelling, shipment and storage will be provided in a reference TOPARP Laboratory Manual for Investigators.**

In some cases the archival tumour blocks will be returned to the local laboratories after the study is complete, depending on local practice. Patients participating on this study will be asked to give permission for possible future research into prostate cancer using these samples. The confidential nature of the tissue and associated data will be fully protected,

and any other research using your tissue will first be reviewed and approved by an ethics committee.

These tumour and plasma samples may be used for, but not restricted to, the elucidation of mechanism of response, understanding the mode of action of olaparib and improving the understanding of disease progression.

15.1 Archival Tumour Blocks and Fresh Biopsies

An adequately sized (minimum of 2 mm x 2 mm) archival tumour tissue paraffin block from resection or a core biopsy from the time of the original diagnosis or from a biopsy / resection of metastatic disease at any time prior to study entry is required. Alternatively, unstained slides prepared from the block can be provided. Mandatory fresh biopsies should be obtained at baseline (during the screening period; anytime between Day-28 to Day1), post commencement of treatment (during Cycle 1; anytime between Day 8 and Day 28) and at study discontinuation. The third biopsy is optional and will be obtained at any point between the patient coming off study treatment to the end of treatment visit.

The fresh tumour biopsy may be obtained from either the prostate or a metastatic site that is safe and amendable to a biopsy. Tumour biopsies may be obtained from the prostate itself (if it has not been surgically resected and has not been treated with radiotherapy) via an ultrasound-guided transrectal biopsy. Local recommendations for the procedure will be followed. Alternative sites where a biopsy can be obtained include lymph nodes, bone or liver where there is evidence of cancer on imaging. Patients who do not have evidence of visceral disease but do have evidence of bone metastasis on the bone scan may undergo a bone biopsy and possible aspirate from the ischium. Ideally, the pre- and post-treatment biopsies will be from the same site. Refer to the TOPARP Laboratory Manual for specific details on sample collection, handling, storage and shipping requirements.

15.2 Circulating Tumour Cell (CTC) Assessments

A total of 18 blood samples will be drawn over 9 study visits for each patient enrolled during the first 12 months of treatment. Baseline samples will be collected at screening and one Cycle 1 Day 1 and subsequently CTC blood samples will be collected at Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, every third cycle thereafter and at time of discontinuation of study treatment. CTCs will be enumerated using Veridex CellSearch™ platform. CTC samples in all patients will be used to enumerate CTC counts and evaluate the molecular profile of tumour cells. Refer to the TOPARP Laboratory Manual for specific details on sample collection, handling, storage and shipping requirements. Amongst the molecular markers that will be studied include:

Immunofluorescence: PTEN, ERG, RAD51, γ H2AX and markers of tumour cell proliferation and cell cycle phase.

FISH: Including *PTEN*, *TMPSS2/ERG*

15.3 Plasma and Urine-Based Biomarkers

Plasma and urine samples for different analyses will be collected at multiple time points during the study (refer to Table 7 for details on the specific samples). These samples will be utilised for the purpose of analysing circulating plasma biomarkers including circulating tumour DNA and RNA for mutational analyses, quantitative real time polymerase chain reaction of ERG detection, plasma proteomic signature, plasma and urine metabolomic studies and microRNA (miRNA) profiles. Proteomic, metabolomic and miRNA profiling may generate signatures that can be used as predictive, prognostic and pharmacodynamic biomarkers that may also be correlated with other study endpoints. Refer to the TOPARP Laboratory Manual for specific details on sample collection, handling, storage and shipping requirements.

Plasma

- **Plasma Metabolomic Profiling:** Blood samples will be obtained at screening, on Cycle 1 Day 1 (-5 min pre-dose and 2hour post-dose), Cycle 1 Day 8 (-5min pre-dose and 2hour post-dose), Day 1 of cycles 2, 3 and 6 (-5 min pre-dose and 2hour post-dose) and at either treatment discontinuation or end of treatment. Patients will be required to fast for at least 8 hours before providing these metabolomic blood samples. During the fasting period water or tea without milk and sugar will be allowed in moderate amounts. For patients who are unable to fast (e.g. insulin dependent diabetic patients) samples should be collected consistently in a non-fasted state. Whenever possible patients should be seen first thing in the morning to limit the burden of fasting. After the blood draw patients will be permitted to have a light breakfast.
- **PAXgene miRNAs Analyses:** Whole blood samples will be collected at screening, Cycle 1 Day 1, and Day 1 of cycles 3 and 5 and at either treatment discontinuation or the end of treatment visit.
- **Plasma Proteomic profiling:** Plasma samples will be obtained at screening, Cycle 1 Day 1 (pre-dose) and at either treatment discontinuation or the end of treatment visit.
- **Circulating Plasma DNA and RNA:** Plasma samples will be collected at screening, Cycle1 Day 1, Cycle 1 Day 8 and on Day 1 of Cycles 2, 3, 5 and at either treatment discontinuation or the end of treatment visit.

Urine

- **Urine Markers of Bone Turnover (telopeptides):** A urine sample collected after the void of the first morning sample will be collected at screening, Day 1 of cycles 1, 3, 6 and at either treatment discontinuation or the end of treatment visit.
- **Urine Metabolomic Profiling:** 24 hour urine samples will be collected at screening, Cycle 1 Day 1, Cycle 1 Day 8 and on Day 1 of Cycles 2, 3 and 6 and at either treatment discontinuation or the end of treatment visit.

The 24 hour urine sample will be collected from the second urine of the previous day until the first urine of the clinic visit day. The urine sample for markers of bone turnover will be collected at the second urine of the clinic visit day.

15.4 Buccal Swabs

A buccal swab will be collected at screening.

15.5 Saliva Collection

A saliva sample will be collected at screening.

15.6 Diffusion-weighted MRI

Diffusion-weighted MRI (DW-MRI) will be performed on an optional basis in a subset of patients. DW-MRI provides better visualisation of tumour cellularity and the results of DW-MRI will be correlated with bone scan results, PSA, CTC counts and patient outcome.

15.7 Rationale of translational research

The intent of the biomarker / translational research embedded in this protocol is outlined below:

- To characterise the molecular profile of prostate cancer and sub-divide this heterogeneous disease.
- To develop predictive biomarkers of olaparib sensitivity which may be utilised to optimise patient selection for future studies
- To correlate the molecular profile of prostate cancer (in particular but not exclusively *PTEN*, *ERG* status by both IHC and FISH analysis) with clinical outcome
- To determine target modulation from olaparib treatment by the generation of γ H2AX foci formation, a marker of DNA damage in fresh biopsies and CTCs
- To evaluate the utility of early changes to CTC counts as a surrogate of clinical benefit to PARP inhibitors in CRPC
- To correlate CTC changes with PSA and radiological responses to olaparib treatment in CRP.

15.8 Whole Genome Sequencing

Samples will be sent to a laboratory approved by the Trial Management Group for genetic testing. Patients will consent to results relevant for the management of their cancer to be reported to them and their clinicians. Patients will be given the option to receive results which are not related to their cancer, but may have potential medical impact for them or significance for biological family members. The feedback of these results may not necessarily be in real-time and only very well known, established signatures will be fed back e.g. BRCA mutations. Principal Investigators should give consideration to using clinical geneticists in the feedback of results to patients.

TIME POINTS	BLOOD BASED BIOMARKERS							URINE BIOMARKERS	
	Saliva	Buccal Swab	CTC	Plasma DNA & RNA Analyses	PAXgene miRNA	Plasma Proteomic Profile	Plasma Metabolomic Profiling (pre and post dose)	Urine Metabolomic profiling	Bone markers of turnover
Screening	X	X	2x10mls	3x10mls	1x2.5mls	1x8.5mls	2x6mls	24 urine collection	Urine collected after the void of the first morning sample
Cycle 1 day 1			2x10mls	3x10mls	1x2.5mls	1x8.5mls	2x6mls	24 urine collection	Urine collected after the void of the first morning sample
Cycle 1 day 8			2x10mls	3x10mls			2x6mls	24 urine collection	
Cycle 1 day 15			2x10mls						
Cycle 2 day1			2x10mls	3x10mls			2x 6mls	24 urine collection	
Cycle 3 day1			2x10mls	3x10mls	1x2.5mls		2x6mls	24 urine collection	Urine collected after the void of the first morning sample
Cycle 4day1			2x10mls						
Cycle 5 day1				3x10mls	1x2.5mls				
Cycle 6 day1							2x6mls	24 urine collection	Urine collected after the void of the first morning sample
Cycle 7day1 & every 3rd cycle thereafter			2x10mls						
End of Treatment Visit			2x10mls	3x10mls	1x2.5mls	1x1mls	2x6mls	24 urine collection	Urine collected after the void of the first morning sample

Table 7: Summary of the blood and urine-based biomarker samples for the translational research

For total volumes of safety and research bloods refer to Appendix J

16 TRIAL MANAGEMENT

The trial will be coordinated by ICR-CTSU in accordance with their quality management system.

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, Co-investigators and identified collaborators, the Trial Statistician and the Trial Managers. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of centres and professional groups. Notwithstanding the legal obligations of the Co-Sponsors and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. Where possible, membership will include a lay/consumer representative. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and will include an independent Chairman (not involved directly in the trial other than as a member of the TSC) and not less than two other independent members. It is the role of the TSC to monitor progress of the trial and to ensure there is adherence to the protocol and the principles of Good Clinical Practice. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16.3 Independent Data Monitoring Committee (IDMC)

An IDMC will be instigated to monitor the progress of the trial. Membership of the IDMC will be proposed by the TMG and approved by the TSC. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU. The IDMC should meet in confidence at regular intervals, firstly to review the safety analysis following the first 5 and 10 patients recruited and at least every 6 months following. A report of the findings and recommendations will be produced following each meeting. This report will be submitted to the TMG and TSC, and if required, the main REC and the MHRA.

The IDMC reserve the right to release any data on outcome or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

17 RESEARCH GOVERNANCE

This Clinical Trial will be conducted in accordance with the ethical principles laid down by the Declaration of Helsinki, 1964 and as amended in 1996 and the principles of Good Clinical Practice.

17.1 Sponsor Responsibilities

The Co-sponsors are The Institute of Cancer Research (ICR) and The Royal Marsden NHS Foundation Trust (RMH). Sponsorship activities and delegated responsibilities are shared between ICR and RMH, in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. Responsibilities of the Co-sponsors are set out in an agreement letter between ICR and RMH.

17.2 Principal Investigator Responsibilities

Responsibilities of each Principal Investigator and participating centre will be detailed in a contract with the Co-sponsors.

Principal Investigator responsibilities include putting and keeping in place arrangements to run the trial at their site according to the trial protocol and applicable guidance notes, The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. The above responsibilities include, but are not limited to, the following:

- Putting and keeping in place arrangements to adhere the principles of GCP
- Keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving and destruction of documentation once the trial has ended as required by regulation 31 of the principal Regulations of the Medicines for Human Use (Clinical Trials) Regulations 2004 implementing the commission directive 2005/28EC
- Ensuring investigational medicinal products (IMPs) are made available to subjects free of charge
- Taking appropriate urgent safety measures and
- Ensuring recording and prompt reporting of SAEs/SARs to ICR-CTSU

ICR is responsible for co-ordinating any required legal agreements and investigator statements.

The delegation of sponsorship responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership

and as such it is necessary to share pertinent information between ICR and RMH/Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

17.3 AstraZeneca Responsibilities

AstraZeneca are responsible on behalf of the co-sponsors for the manufacture, packing, labelling and distributing of study drug and matching placebo to site in accordance with Good Manufacturing Practice and all applicable local legislation. Some of these responsibilities have been delegated by AstraZeneca to Fisher Clinical Services. Responsibilities are defined in an agreement between AstraZeneca and the co-sponsors, and AstraZeneca and Fisher Clinical Services.

18 TRIAL ADMINISTRATION & LOGISTICS

18.1 Protocol Compliance

The TOPARP Trial is being conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the EU Clinical Trials Directive. Before activating the trial, participating centres are required to sign an agreement accepting responsibility for all trial activity which takes place within their centre.

Sites may commence recruitment once centre agreements have been signed by both parties, trial documentation is in place and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

18.2 Data Acquisition

ICR-CTSU is responsible for the data management and statistical analysis of trial data. Electronic (e) Case Report Forms (eCRF) will be used for the collection of trial specific data. The Trial Management Group reserves the right to amend or add to the eCRF as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres in accordance with the guidelines provided by ICR-CTSU.

The clinical data should be recorded in the TOPARP eCRFs in a timely manner.

By participating in the TOPARP trial, the Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure that:

- Sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and eCRFs;
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- All staff at their centre who are involved with the trial will meet the requirements of the EU Directive;
- Original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent;
- All essential documents must be retained for five years after the Trial ends to comply with current legislation.
- Staff will comply with the protocol and Trial Guidance Notes for the TOPARP trial.

Completion of eCRFs will be monitored by ICR-CTSU and any missing forms will be reported to the originating site.

18.3 Central Data Monitoring

Once data has been entered by the site personnel on the eCRF, the ICR-CTSUs will review and check the data for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be issued to the centre for resolution.

Data will be further reviewed for data anomalies / missing data, by central statistical monitoring. Any systematic inconsistencies identified may trigger monitoring visits to centres.

18.4 On-Site Monitoring

Site monitoring will be conducted at participating centres at least once during the course of the trial. Additional on-site monitoring may be triggered by routine central statistical monitoring or identification of a new risk to the trial.

If a monitoring visit is required, ICR-CTSUs will contact the centre to discuss dates of proposed visit. Once a date has been confirmed, the centre should ensure that the relevant patient notes are available for monitoring.

If any problems are detected in the course of the monitoring visit, ICR-CTSUs will work with the Principal Investigator to resolve issues and, if necessary, to determine the centre's future participation in the study.

ICR-CTSUs staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the site agreement and trial protocol to ensure the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996.

18.5 End of trial

The end of trial for MHRA and MREC purposes is the date of last data capture

18.6 Archiving

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. They should be retained for a sufficient period (at least 5 years after the date of last date of data capture) for possible inspection by the regulatory authorities. Documents should be securely stored and access restricted to authorised personnel.

19 PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

The trial will have received ethical, regulatory and institution specific approvals prior to recruitment of any patients into the study. Before entering patients, the Principal Investigator at each site is responsible for gaining Site Specific Assessment and Research and Development approval of this protocol.

Patients should be asked to sign the trial consent forms after receiving both verbal and written information about the trial. All consent forms must be countersigned by the Principal Investigator or a designated individual. A record listing the designated individuals and the circumstances under which they may countersign consent forms must be clearly documented at the research site as part of the Delegation of Responsibilities Log. This log, together with original copies of all signed patient consent forms, must be available for inspection.

The TOPARP patient information sheets should be provided in addition to any standard patient information sheets that are provided by the centre and used in routine practice.

19.1 Patient Confidentiality

Patients will be asked to consent to their full name being collected at registration in addition to their date of birth, hospital number, postcode and NHS number (CHI in Scotland) to allow tracing through national records to assist with long term follow up and to allow linkage with routinely collected NHS data. The personal data recorded on all documents will be regarded as confidential, and any information which would allow individual patients to be identified will not be released into the public domain.

Each investigator should keep a separate log of all patients' Trial IDs, names, addresses and hospital numbers. The investigator must maintain trial documents, which are to be held at the participating centres (e.g. patients' written consent forms), in strict confidence. The investigator must ensure the patients' confidentiality is maintained.

ICR-CTSU will maintain the confidentiality of all patients and will not reproduce or disclose any information by which patients could be identified. Representatives of ICR-CTSU and the regulatory authorities will be required to have access to patients notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries it is also necessary to have access to the complete study records provided that patient confidentiality is protected.

19.2 Data Protection

ICR-CTSU will comply with all applicable data protection laws. Any requests from patients for access to data about them held at ICR-CTSU should be directed to the Trial Manager in

the first instance who will refer the request to the Data Protection Officer at The Institute of Cancer Research.

19.3 Liability

The Co-Sponsors have taken out an insurance policy to cover their study responsibilities, and certification of this will be provided to the regulatory authorities as required. ICR-CTSU will need to be satisfied that all participating sites have appropriate indemnity arrangements in place.

20 FINANCIAL MATTERS

The trial is investigator designed and led and has been approved by Clinical Trials Advisory & Awards Committee (CTAAC) of Cancer Research UK, and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

ICR has received funding from Cancer Research UK and AstraZeneca (via the AstraZeneca/NCRN collaboration) for the central coordination of the trial. AstraZeneca are also providing olaparib for the purposes of this trial free of charge.

In the UK, the trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research (NIHR) portfolio by virtue of its approval by CTAAC. Therefore, National Cancer Research Network (NCRN) resources should be made available for the TOPARP trial to cover UK specific research costs.

21 PUBLICATION POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group led by the chief investigator, appointed from amongst the Trial Management Group, and participating clinicians. All participating centres and clinicians will be acknowledged in this publication together with the dedicated staff from the ICR-CTSU. All presentations and publications relating to the trial must be authorised by the Trial Management Group, on whose behalf publications should usually be made. Authorship of any secondary publications e.g. relating to the various biological studies will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to the TOPARP trial without prior permission from the Trial Management Group.

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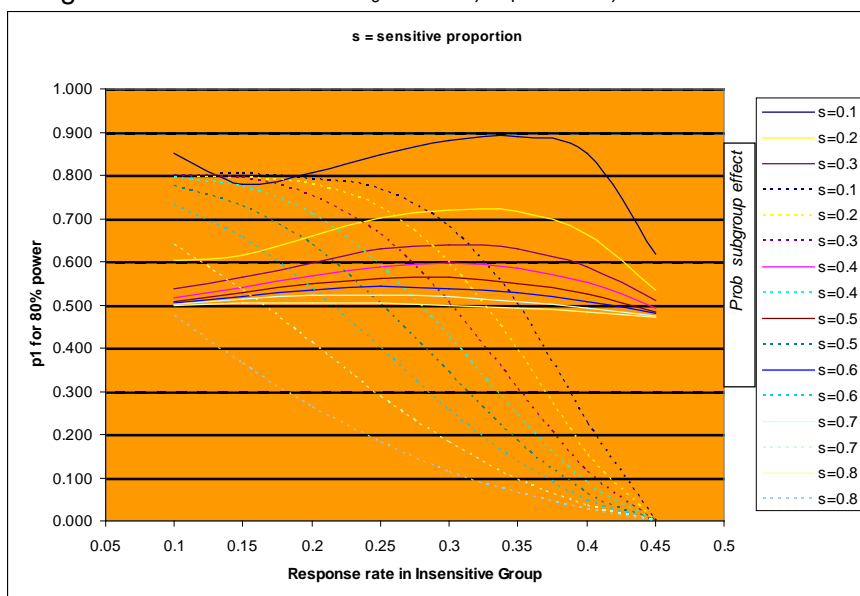
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23 APPENDICES

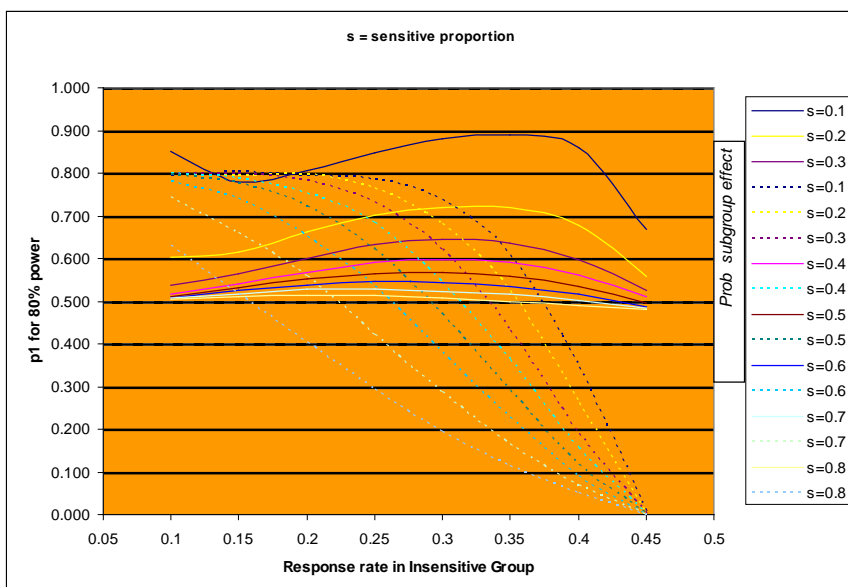
23.1 Appendix A: Detectable Effects

It is possible to calculate detectable effects in the sensitive group (80% power, y-axis) based on the proportion of sensitive patients (individual lines) and the response rate (x-axis) in the insensitive subgroup. Also shown is the probability a subgroup effect is detected (dashed lines), with 80% power this probability cannot exceed 80%. The fall in the probability of detecting a subgroup effect with increasing response rate in insensitive patients is therefore balanced by an increase in the probability of detecting an overall effect. Thus, in the extreme, if the response rate in insensitive patients is 45% and the response rate in sensitive patients is about 50% a conclusion of overall efficacy will be reached with 80% power, for subgroups of size 30% or more.

Using cut offs for Part A of $a_0=15/30$, $a_1=23/45$, as intended.



Using cut offs for Part A of $a_0=18/30$, $a_1=27/45$ the probability of detecting a subgroup effect if the sensitive group is large (>50%) can be improved.



23.2 Appendix B: Sample Size Calculations

TOPARP sample size calculations, **Part A** : alpha 2.2%, Power 90%

Ho : Null Hypothesis Response rate (p0) is 5%

Probability reject **0.97818** *alpha* 2.2%

Reject first stage **0.81218** (Probability of early termination, sum of values in light blue)

Reject second stage **0.166** (sum of values in dark blue)

sum 0.97818

N	po	N second stage														
First	0.05	0	1	2	3	4	5	6	7	8	15				
0	0.214639															
1	0.338903	0														
2	0.258637	0.46329	0.3657562	0.13475	0.03073	0.00485	0.00056	4.9E-05	3.3E-06	1.8E-07	3.1E-20				
3	0.12705	0.059	0.046	0.017	0.004	0.001	0	0	0	0		0				
4	0.045136	0.021	0.017	0.006	0.001	0	0	0	0	0		0				
5	0.012353	0.006	0.005	0.002	0	0	0	0	0	0		0				
6	0.002709	0.001	0.001	0	0	0	0	0	0	0		0				
7	0.000489	0	0	0	0	0	0	0	0	0		0				
8	7.4E-05	0	0	0	0	0	0	0	0	0		0				
9	9.52E-06	0	0	0	0	0	0	0	0	0		0				
10	1.05E-06	0	0	0	0	0	0	0	0	0		0				
11	1.01E-07	0	0	0	0	0	0	0	0	0		0				
12	8.39E-09	0	0	0	0	0	0	0	0	0		0				
13	6.11E-10	0	0	0	0	0	0	0	0	0		0				
14	3.91E-11	0	0	0	0	0	0	0	0	0		0				
15	2.19E-12															
16	1.08E-13															
17	4.69E-15															
18	1.78E-16															
.....																
26	3.33E-30															
27	2.59E-32															
28	1.46E-34															
29	5.31E-37															
30	9.31E-40															

Stage I 2.31E-12
probability of incorrect stopping

H1 : Null Hypothesis Response rate (p1) is 20%

Probability reject **0.10318** *Power* 89.7%

Reject first stage **0.04418** (Probability of early termination, sum of values in light blue)

Reject second stage **0.059** (sum of values in dark blue)

N	po	N second stage														
First	0.2	0	1	2	3	4	5	6	7	8	15				
0	0.001238															
1	0.009285															
2	0.033656	0.03518	0.1319414	0.2309	0.25014	0.1876	0.10318	0.04299	0.01382	0.00345	3.3E-11				
3	0.078532	0.003	0.01	0.018	0.02	0.015	0.008	0.003	0.001	0		0				
4	0.132522	0.005	0.017	0.031	0.033	0.025	0.014	0.006	0.002	0		0				
5	0.172279	0.006	0.023	0.04	0.043	0.032	0.018	0.007	0.002	0.001		0				
6	0.179457	0.006	0.024	0.041	0.045	0.034	0.019	0.008	0.002	0.001		0				
7	0.153821	0.005	0.02	0.036	0.038	0.029	0.016	0.007	0.002	0.001		0				
8	0.110559	0.004	0.015	0.026	0.028	0.021	0.011	0.005	0.002	0		0				
9	0.067564	0.002	0.009	0.016	0.017	0.013	0.007	0.003	0.001	0		0				
10	0.035471	0.001	0.005	0.008	0.009	0.007	0.004	0.002	0	0		0				
11	0.016123	0.001	0.002	0.004	0.004	0.003	0.002	0.001	0	0		0				
12	0.006382	0	0.001	0.001	0.002	0.001	0.001	0	0	0		0				
13	0.002209	0	0	0.001	0.001	0	0	0	0	0		0				
14	0.000671	0	0	0	0	0	0	0	0	0		0				
15	0.000179															
16	4.19E-05															
17	8.63E-06															
18	1.56E-06															
.....																
26	7.53E-15															
27	2.79E-16															
28	7.47E-18															
29	1.29E-19															
30	1.07E-21															

Stage I 0.000231
probability of incorrect stopping

TOPARP sample size calculations, **Part A**, rule to be applied if no subgroup is found:

Ho : Null Hypothesis Response rate (p0) is 30%

<u>N</u>	<u>p0</u> 0.3	Reject first stage	0.94505 (sum of values in light blue)	alpha	5.5%
0	1.07E-07	16	0.0896266	32	1.3E-08
1	2.06E-06	17	0.0655253	33	2.2E-09
2	1.95E-05	18	0.0436835	34	3.3E-10
3	0.00012	19	0.0266043	35	4.5E-11
4	0.000538	20	0.0148224	36	5.4E-12
5	0.00189	21	0.0075624	37	5.6E-13
6	0.005401	22	0.0035357	38	5E-14
7	0.012895	23	0.0015153	39	3.9E-15
8	0.026251	24	0.0005953	40	2.5E-16
9	0.046252	25	0.0002143	41	1.3E-17
10	0.071361	26	7.065E-05	42	5.3E-19
11	0.09731	27	2.131E-05	43	1.6E-20
12	0.118162	28	5.87E-06	44	3.1E-22
13	0.12855	29	1.475E-06	45	3E-24
14	0.125927	30	3.371E-07		
15	0.111535	31	6.991E-08		

Ha : Alternate Hypothesis Response rate (p1) is 50%

<u>N</u>	<u>p1</u> 0.5	Reject first stage	0.11635	Power	88.4%
0	2.84E-14	16	0.0183782	32	0.00207
1	1.28E-12	17	0.0313511	33	0.00082
2	2.81E-11	18	0.0487684	34	0.00029
3	4.03E-10	19	0.0693024	35	9.1E-05
4	4.23E-09	20	0.0900931	36	2.5E-05
5	3.47E-08	21	0.1072537	37	6.1E-06
6	2.31E-07	22	0.1170041	38	1.3E-06
7	1.29E-06	23	0.1170041	39	2.3E-07
8	6.13E-06	24	0.1072537	40	3.5E-08
9	2.52E-05	25	0.0900931	41	4.2E-09
10	9.07E-05	26	0.0693024	42	4E-10
11	0.000288	27	0.0487684	43	2.8E-11
12	0.000817	28	0.0313511	44	1.3E-12
13	0.002075	29	0.0183782		
14	0.004743	30	0.0098017		
15	0.009802	31	0.0047428		

TOPARP sample size calculations, **Part B** :

Ho : Null Hypothesis Response rate (p0) is 30%

<u>N</u>	<u>p0</u> 0.3	Reject first stage	0.95628 (sum of values in light blue)	alpha	5%
0	1.53E-07	16	0.0825133	32	5.4E-09
1	2.88E-06	17	0.0582447	33	8.4E-10
2	2.66E-05	18	0.037443	34	1.2E-10
3	0.000159	19	0.0219591	35	1.4E-11
4	0.0007	20	0.0117638	36	1.5E-12
5	0.0024	21	0.0057619	37	1.4E-13
6	0.006687	22	0.0025816	38	1.1E-14
7	0.015556	23	0.0010583	39	7.4E-16
8	0.030835	24	0.0003969	40	4E-17
9	0.05286	25	0.0001361	41	1.7E-18
10	0.07929	26	4.261E-05	42	5.1E-20
11	0.105033	27	1.218E-05	43	1E-21
12	0.123789	28	3.168E-06	44	9.8E-24
13	0.130591	29	7.491E-07		
14	0.123928	30	1.605E-07		
15	0.106224	31	3.107E-08		

Ha : Alternate Hypothesis Response rate (p1) is 50%

<u>N</u>	<u>p1</u> 0.5	Reject first stage	0.14561	Power	85%
0	5.68E-14	16	0.0236875	32	0.0012
1	2.5E-12	17	0.0390147	33	0.00044
2	5.38E-11	18	0.058522	34	0.00014
3	7.53E-10	19	0.0800828	35	4E-05
4	7.72E-09	20	0.1001035	36	1E-05
5	6.17E-08	21	0.114404	37	2.2E-06
6	4.01E-07	22	0.1196042	38	4E-07
7	2.18E-06	23	0.114404	39	6.2E-08
8	1.01E-05	24	0.1001035	40	7.7E-09
9	4.03E-05	25	0.0800828	41	7.5E-10
10	0.000141	26	0.058522	42	5.4E-11
11	0.000436	27	0.0390147	43	2.5E-12
12	0.001199	28	0.0236875	44	5.7E-14
13	0.002951	29	0.013069		
14	0.006534	30	0.0065345		
15	0.013069	31	0.0029511		

23.3 Appendix C: Evidence of PD to Determine Trial Entry Eligibility

Patients being considered for trial entry should have evidence of disease progression by either PSA, modified RECIST or bone scan to be eligible.

PSA: PSA evidence of disease progression based on the prostate cancer working group (PCWG) 2 criteria consist of a minimum PSA level 2.0 ng/ml that has risen on at least 2 successive occasions, at least 1 weeks apart. The reference value # 1 is the last value before the rise in PSA was observed. If the confirmatory PSA value (Figure 5, # 3A) is greater than the screening value then progression by PSA is met and the patient is eligible for trial enrolment on the basis of PSA alone. If the confirmatory PSA (Figure 5, #3B) value is less than the screening PSA (Figure 5, #2) value, then an additional test for rising PSA (#4) will be required to document progression before the patient can be enrolled.

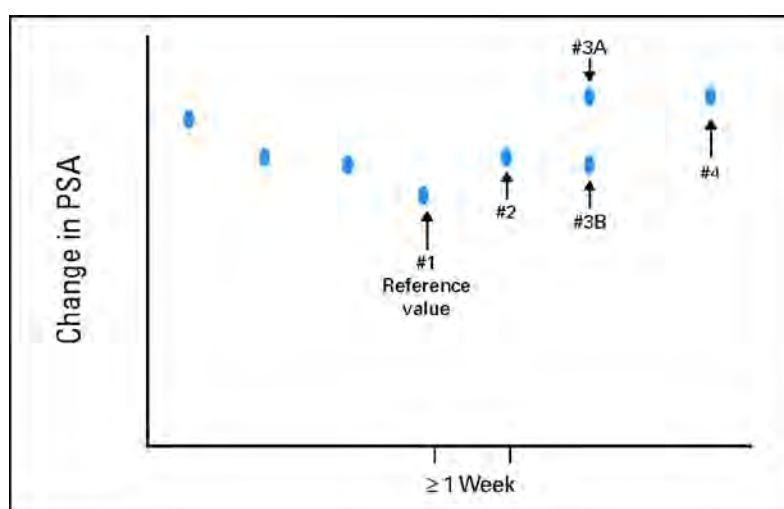


Figure 5: Eligibility Based on PSA

Target lesion/measurable disease: Patients are not required to have evidence of disease progression by measurable disease if they meet the criteria for disease progression on the basis of PSA or bone scan. Evidence of nodal or visceral disease RECIST progression however is sufficient for trial entry independent of PSA readings. Because lymph nodes may be enlarged due to benign pathology, only lymph nodes that are ≥ 2 cm should be used for disease evaluation.

Bone scan: Evidence of disease progression based on bone scan appearance is sufficient for trial entry independent of PSA readings. If the appearance of the bone scan is the only indicator of progression then there must be ≥ 2 new bone lesions compared with the prior bone scans. If there is ambiguity about the appearance of the bony lesions such as traumatic in nature or secondary to a flare reaction then it is recommended that an alternative imaging modality such as MRI or fine-cut CT be used to evaluate these lesions further.

23.4 Appendix D: Outcome Measures of Response / Progression Post Study Treatment

Procedures for Assessing PSA Response / Progression Post Study Treatment

PSA measurements will be done every 12 weeks on day1 of cycle 4,7,10 and every 3rd cycle thereafter. Increases and decreases will be tracked in order to assess disease response. The PSA readings on its own will not be used to define progression in this protocol. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG 2:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA from cycle1day1 (baseline) PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. The first PSA reading will be obtained at week 12.

Duration of PSA Response:

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the Cycle 1 Day 1 (baseline) value that has been confirmed by a second value until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be assessed at the last PSA measurement.

Time to PSA Progression:

For patients who have achieved a $\geq 50\%$ decrease from the Cycle 1 Day 1 (baseline), the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 4 or more weeks later. For patients without a PSA decrease of this magnitude or without a decrease, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented, which is confirmed by a second consecutive value 4 or more weeks later.

Procedures for Assessing Radiological Responses / Progression Post Study Treatment

Categorisation of response in this study will be based on modified RECIST 1.1 for soft tissue disease and appearance of bone scan for bone metastasis.

Bone metastasis evaluation:

The first bone scan should not be performed before 12 weeks post commencement of treatment unless clinically indicated as there may be evidence of a flare response early on which may confuse the response evaluation. A patient will be considered to have progressed on bone scan if the following criteria are met:

- If the first bone scan with 2 new lesions is observed ≤ 13 weeks from the point of Cycle 1 Day 1 and is confirmed by a follow up scan ≥ 6 weeks later showing 2 additional new lesions (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan).
- The first bone scan with ≥ 2 new lesions compared with baseline is observed > 13 weeks from Cycle 1 Day 1 and the new lesions are verified on the next bone scan ≥ 6 weeks later (i.e. a total of ≥ 2 new lesions compared with baseline). If the second scan confirms progression the data of the progression is the date of the first bone scan rather than the second confirmatory scan.

Measurable Disease Evaluation:

Changes in nodal and visceral disease should be recorded using the modified RECIST criteria defined in Appendix E.

Table 8: Radiological Criteria for Ascribing Disease Progression

Evidence of Progression	Confirmation	Action
Bone Disease Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment ≤ 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show an additional 2 new lesions compared to the first post treatment scan (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment > 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should confirm the presence of the 2 new lesions compared the baseline scan. (i.e. a total of ≥ 2 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Soft Tissue Disease as defined by RECIST on CT/MRI	Progression at any scheduled reassessment ≥ 12 weeks does not need to be confirmed.	Investigators are highly encouraged to maintain the patient's treatment with study medication unless radiological progression is observed.

Progression Free Survival (PFS)

In this protocol death, radiographic and unequivocal clinical progression comprise the PFS events. PFS is defined from the time of study entry to confirmed disease progression based on either:

- Radiological progression as documented on bone scans and / or measurable disease on CT scans

OR

- Unequivocal clinical progression

OR

- Death

The analysis of PFS is based on the time of the first progression observed. Where possible all disease assessment (Bone scan, CT, PSA) should be collected at the same time points.

23.5 Appendix E: Modified RECIST

The primary efficacy objective to this trial is based on tumour assessment. For the purpose of this study, definitions of soft tissue tumour assessments will be based on a Modified Response Evaluation Criteria in Solid Tumours 1.1 (RECIST1.1). Pertinent points are summarised below.

Evaluation of measurable and non-measurable lesions

1. **Measurable lesions** – lesions that can be accurately measured in at least one dimension with the longest diameter \geq 20 mm using conventional techniques or \geq 10 mm, with a spiral CT scan.
2. **Non-measurable lesions** – all other lesions, including small lesions (longest diameter \leq 10 mm, with a spiral CT scan), i.e., blastic bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
3. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, should not be included in assessment of response, but should be assessed for progression.
4. For this study, bone lesions are not considered “non-measurable” lesions for RECIST. Bone lesions will be assessed by bone scan only.
5. All measurements should be taken and recorded in metric notation, using a ruler or calipers. Preferably, all screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.
6. The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up.
7. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion is recommended.

Methods of measurement:

1. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.

2. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung, however CT scans are preferable.
3. Ultrasound (US), endoscopy and laparoscopy should not be used to measure tumour lesions. It is however a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound may also be used to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
4. Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions).

Baseline documentation of target and non-target lesions

1. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline and at the time points specified in the protocol.
2. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements.
3. A sum of the longest diameters (LD) for all target lesions will be calculated and reported as the baseline sum of LD. The baseline sum LD will be used as reference by which to characterise the objective tumour response.
4. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions will also be monitored throughout the study, and an overall assessment of response will be made. Details of any new lesions will also be recorded. It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Table 9: Response Criteria

Response criteria	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD)	At least 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	Whether sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Table 10: Responses in patients with both target and non-target disease

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/nonPD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD= progressive disease, NE= inevaluable

Table 11: Responses in patients with only non-target disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/nonPD	No	Non-CR/nonPD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD= progressive disease, NE= inevaluable

Reproduced from: <http://www.recist.com/recist-comparative/01.html> and Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 12 weeks) that is defined in the study protocol.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

23.6 Appendix F: ECOG Performance Status

Table 12: ECOG Performance Status

ECOG Performance Status	Function
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead


23.7 Appendix G: National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.02)

V4.02 (CTCAE): publish date August 9, 2010:
ctep.cancer.gov/reporting/ctc.html

23.8 Appendix H: World Medical Association Declaration of Helsinki

<http://www.wma.net/e/policy/b3.html>

23.9 Appendix I: Brief Pain Inventory (Short Form)

 1903	Date: <input type="text"/> / <input type="text"/> / <input type="text"/> (month) (day) (year)	Study Name: _____ Protocol #: _____ PI: _____ Revision: 07/01/05
Subject's Initials: _____ Study Subject #: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		

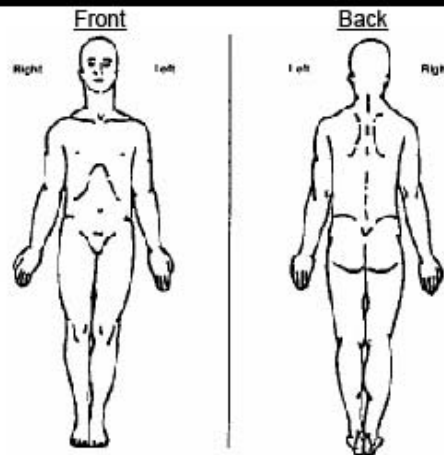
PLEASE USE BLACK INK PEN

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the **average**.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain As Bad As You Can Imagine

23.10 Appendix J: Total blood volumes drawn at each time point

Study time points	Months on study	Total volume of safety and research bloods per month
Screening	-1	92.5mls
Cycle 1 Day 1	1	156.5 mls
Cycle 1 Day 8		
Cycle 1 Day 15		
Cycle 2 Day 1	2	74mls
Cycle 3 Day 1	3	76.5mls
Cycle 4 Day 1	4	38mls
Cycle 5 Day 1	5	44.5mls
Cycle 6 Day 1	6	24mls
Cycle 7 Day 1	7	38mls
Cycle 8 Day 1	8	12mls
Cycle 9 Day 1	9	12mls
Cycle 10 Day 1	10	38mls
Cycle 11 Day 1	11	12mls
Cycle 12 Day 1	12	12mls
End of study		92.5mls

Summary of Protocol Amendments

Amendment 1 – Protocol version 2, 6th March 2012

This amendment to the protocol and PIS followed discussions between the protocol development group and AstraZeneca (manufacturer of Olaparib) regarding the dose of Olaparib to use within TOPARP. In taking forward the olaparib dose of 400mg bd it was agreed the IDMC would perform a safety review after the first 5 and 10 patients have completed 1 cycle of treatment to ensure the dose of drug is well tolerated in the trial population and that any safety concerns are identified at the beginning of the trial. Additionally clarifications were made to visits and long term follow up of patients.

Amendment 2 – Protocol version 3, 12th November 2012

Amendment to the protocol, PIS and investigators brochure submitted following the release of Edition 8 of the Olaparib Investigators Brochure which updated the drug toxicity profile and changes to how the drug olaparib should be administered. Additionally clarifications were made to the biological sampling requirements.

Amendment 3 – Protocol version 4, 15th April 2014

Amendment to the protocol, PIS, CF and investigators brochure submitted which includes the extension of the CTC screening window from 14 to 28 days prior to cycle 1 day 1, the addition of whole genome sequencing and the use of tissue, blood and urine samples for research within the trial which have been taken prior to trial specific TOPARP consent.



TOPARP

Phase II Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer

Statistical Analysis Plan
Final version 2.0

18/02/2015

This statistical analysis plan is based on protocol version 4.0 [15th April 2014]

REC reference no: 11/LO/2019

CR UK (other funder) no: CRUK/C12540/A12354

EudraCT no: 2011-000601-49

ICR-CTSU no: ICR-CTSU/2011/10030

CTA reference no: 22138/0016/001/0001

The current draft version of SAP if prior to principal analysis of primary endpoint, any previous draft versions used for formal presentation, i.e. peer reviewed conference posters/presentations prior to the principal analysis, and any final version(s) of the SAP will be stored in the Statistical Section of the Trial Master File

This statistical analysis plan is a framework to guide statistical analysis and may be supplemented by additional and exploratory analyses. Trial statisticians reserve the right to amend analysis methods as appropriate after discussion with the ICR-CTSU Scientific Lead.

For final versions only:

This statistical analysis plan has been approved by the following personnel:

Trial Statistician: Roger A'Hern / Eleftheria Kalaitzaki / Helen Mossop / Nuria Porta

Signed: H. Mossop

Date: 11/3/15

ICR-CTSU Scientific Lead: Emma Hall

Signed: EHall

Date: 11/3/15

Chief Investigator: Johann de Bono

Signed: JdB

Date: 28/3/2015

Document history

Version	Date	Changes made
1.0	03/10/2012	First draft
1.1	22/12/14	Update on continuing recruitment to stage 2 of part A. Amended wording for confirmation of CTC response.
2.0	18/02/2015	Update on evaluable patient population. Removal of biomarker analysis details.

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1 Introduction

This statistical analysis plan provides guidelines for the presentation, analysis and publication for the TOPARP trial. This plan, along with all other documents relating to the analysis of this trial, will be stored in the Statistical section of the Trial Master File.

It is intended that the results reported in these papers will not divert from the strategy set out here; subsequent papers of a more exploratory nature will not be bound by this strategy- though they are expected to follow the broad principles laid down for the main papers. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit sensible practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available for information and can be viewed at request. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Procedures for monitoring data accuracy and data entry quality are provided in the central statistical monitoring plan and are not reproduced here.

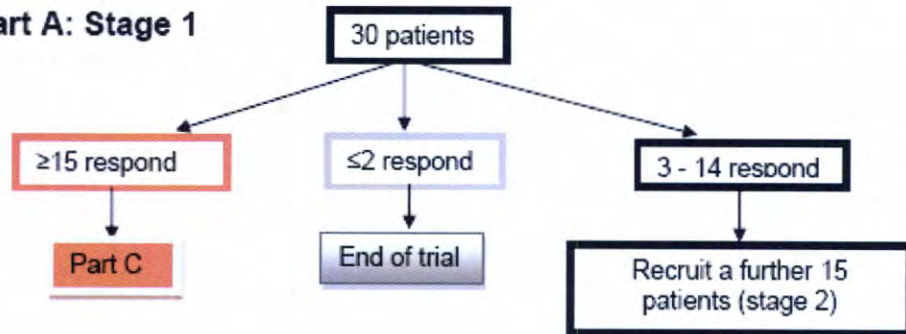
1.1 Trial design

TOPARP is a single arm, multi-centre, open label, two-stage phase II clinical trial addressing the hypothesis that olaparib will improve the response for patients with advanced CRPC who have failed androgen deprivation and taxane-based treatment.

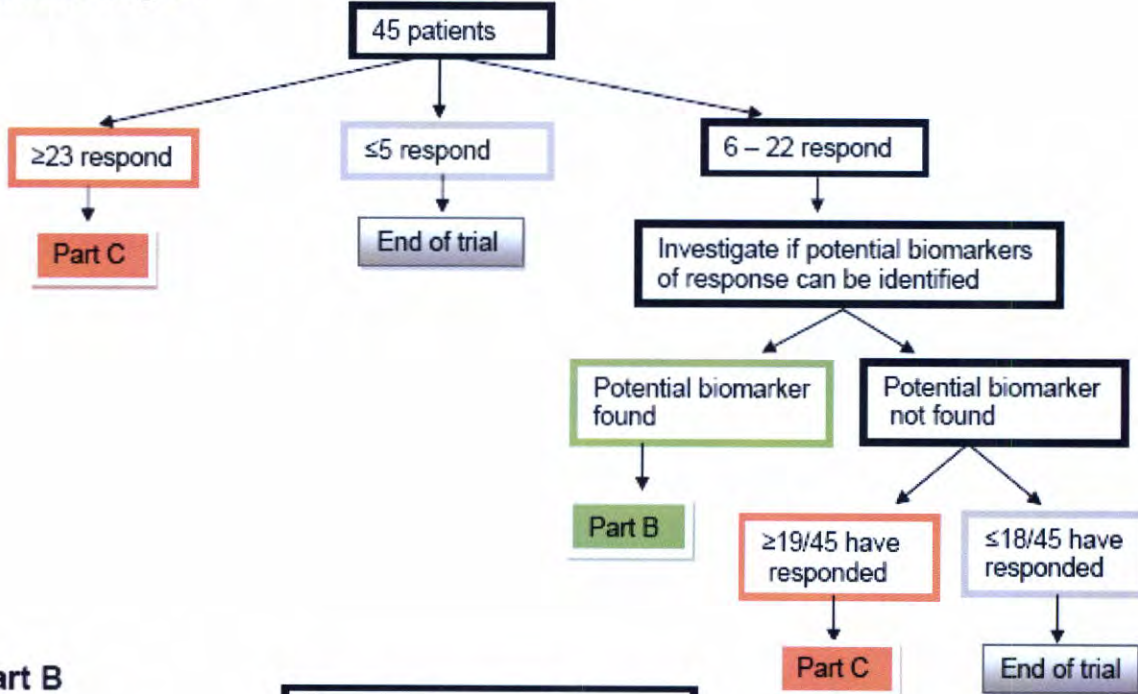
The study is divided into 2 parts. Part A is an efficacy screening stage for sensitive biomarkers. It is designed as an open-labelled, non-randomised two stage design both to allow the activity of olaparib in unselected advanced CRPC patients to be evaluated and to permit the development of predictive biomarkers of response to olaparib. Part B is a subsequent validation stage which will be undertaken if confirmation of activity in a biomarker defined subgroup is necessary. It is an open-labelled, single stage assessment of anti-tumour activity of olaparib in preselected patients based on putative biomarkers of Homologous Recombination (HR) repair deficiency previously identified in Part A. At least 89 evaluable patients will be enrolled to Parts A & B.

Patients will be administered oral olaparib tablets, 400mg BID continuously until disease progression is documented and confirmed (i.e. confirmed radiographic progression) or withdrawal for another reason.

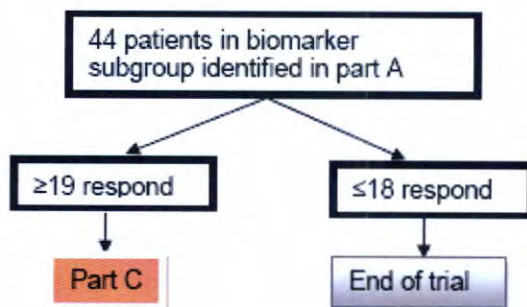
Part A: Stage 1



Part A: Stage 2



Part B



Part C will only be initiated if the anti-tumour activity observed in Parts A and B are sufficient to warrant a randomised study. The design of Part C will be determined following the analysis of Parts A/B.

1.2 Study population

Subjects with advanced progressing CRPC who have had either one or two previous lines of taxane-based chemotherapy will be invited to participate in the TOPARP study.

Inclusion Criteria

Each patient must meet the following criteria to be enrolled in the study:

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 taxane-based 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:
 - At least 28 days since the completion of prior flutamide treatment. Patients whose PSA did not decline in response to antiandrogens given as a second line or later intervention will only require a 14 days washout prior to Cycle 1, Day 1.
 - 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.
 - 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:
 - 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 glucocorticoids for control of symptoms must have documented PSA progression by PCWG22 while on systemic glucocorticoids prior to commencing Cycle1 Day1 of treatment.
 - 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 orchidectomy), 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 \geq 50%)
9. Life expectancy $>$ 12 weeks.
10. Patient must be able to swallow a whole tablet.

11. Patient and the patient's partner of childbearing potential, must agree to use medically accepted methods of contraception (e.g., 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 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:
 - Haemoglobin ≥ 10 g/dL independent of transfusions
 - White blood cells $> 3 \times 10^9$ /L
 - Absolute neutrophil count $\geq 1.5 \times 10^9$ /L
 - Platelets $\geq 100 \times 10^9$ /L
 - Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) except for patients with known Gilbert's syndrome.
 - 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.
 - 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:

$$\text{GFR} = \text{CrCl (ml/min)} = (140 - \text{age}) \times \text{wt (kg)} / (\text{serum creatinine} \times 72)$$
 - Albumin > 25 g/dl

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

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 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 have experienced a seizure or seizures within 6 months of study treatment or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic 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 investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's 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

2.0 Trial Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the anti-tumour activity of olaparib in patients with advanced CRPC who have progressed following one or two chemotherapy regimens including taxane-based regimens.

2.2 Secondary Objectives

The secondary objectives are to evaluate:

- Radiological progression-free survival (rPFS)
- Time to radiological progression
- Progression free survival (PFS)
- Overall survival
- Time to PSA progression
- Duration of PSA response (decline of $\geq 50\%$)
- PSA objective response (PSA-ORR)
- The utility of CTCs as an early indication of benefit from PARPi therapy
- Further characterise the safety profile of olaparib in advanced CRPC patients

2.3 Tertiary/exploratory Objectives

- To evaluate clinical benefit as indicated by an improvement in pain measurements (BRI-SW)

- To evaluate DW-MRI imaging in selected patients and to correlate these results with PSA, CTC and radiological responses by conventional imaging

3.0 Sample size & power

The aim is to identify a sensitive subgroup with a 50% response rate on the basis that high response rates are necessary to be confident of demonstrating a survival benefit, the primary goal of the phase II strategy (See Appendix A and B).

Part A (comprised of stages 1 & 2)

The screening trial will involve all comers (unselected patients) and is an open-labelled, multi-centre two-stage design based on $H_0: p_0=0.05$; $H_a: p_1=0.20$; $\alpha=0.02$ and $\beta=0.10$. It will recruit a **maximum of 45 patients** (30 in stage 1 and 15 in stage 2) with an initial efficacy level of 20% and an inefficacy level of 5%, to allow for the fact that only a small subset of patients may be sensitive to olaparib. This part will evaluate the anti-tumour activity of olaparib in unselected CRPC patients and will identify potential biomarkers of response.

→ Stage 1

The first stage will enrol 30 patients and when all 30 have been followed up for a minimum of 6 months, or have been assessed for the primary endpoint, an interim analysis will take place to evaluate the response rate. In the absence of any safety concerns recruitment will continue to part A stage 2 whilst response data on the first 30 patients accumulates.

Given the efficacy level of 20% and inefficacy level of 5% the trial will be terminated with the conclusion of inefficacy if there are **2 or fewer responses**. If there are **15 or more responses** in the first stage, broad efficacy will be concluded and no more patients will be entered and Part C will commence in unselected patients. If between **3 to 14 patients respond**, patient accrual will continue to a total of 45 patients (stage 2) and an investigation into the identification of a potential biomarker of response will be carried out.

→ Stage 2

If the trial progresses to stage 2, a further 15 patients will be recruited, giving a total of 45 patients for part A. An interim analysis will be triggered once 45 patients have been followed up for a minimum of 6 months, have been assessed for the primary endpoint, or alternatively we observe 23 or more responses. The recruitment will be halted. If **23 or more** patients respond, Part C will be initiated. If **5 or fewer patients** respond, the null hypothesis will be accepted and the study will be terminated. If **between 6 and 22 patients respond**, an investigation into the identification of potential biomarkers of response will be carried out. If a potential biomarker subgroup is found, Part B will be undertaken. If a subgroup is not found, then Part C will be undertaken if at least 19 of the patients have responded, otherwise the study will be terminated

since sufficient activity has not been observed based on $H_0: p_0=0.3$; H_a ; $p_1=0.5$; $\alpha=0.059$ and $\beta=0.11$.

4.0 Randomisation/ recruitment procedures

Patients who meet the eligibility and screening requirements (including pre-dose biopsy, blood samples and CTCs) will be enrolled to the study. For both parts A & B there will be only 1 treatment arm, olaparib.

5.0 Endpoints

5.1 Primary Endpoint

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

- Objective response by modified RECIST (baseline lymph node size must be ≥ 2 cm to be considered a target lesion) or
- Conversion of circulating tumour cell count (CTC) from $\geq 5/7.5$ ml blood at baseline to $< 5/7.5$ ml blood nadir confirmed by a second consecutive value obtained four or more weeks later or
- PSA decline of $\geq 50\%$ (according to the PCWG2)

Evaluable patients with no confirmed response as defined above will be classified as non-responders.

5.2 Secondary Endpoints

- PSA response and PSA progression
- Time-to-PSA Progression
- Duration of PSA response
- PSA objective response rate (PSA-ORR)
- Pattern of PSA Responses
- CTC Response
- Radiographic Progression Free Survival (rPFS)
- Time to Radiographic Progression
- Progression Free Survival (PFS)
- Overall Survival (OS)

5.3 Tertiary/exploratory Endpoints

- Pain palliation
- Safety of olaparib
- Impact of treatment with olaparib on bone metastases imaging by DW-MRI

6.0 Data completeness and consistency

6.1 Patient flow through trial

As part of the principal analysis of the primary endpoint for publication a CONSORT diagram will be provided. This will include the number of patients available for the efficacy population and safety population and the number of patients who discontinued with trial treatment and reasons for discontinuation.

6.2 Compliance with the assessments

Compliance with trial treatment, safety and follow-up will be assessed by the IDMC (via tables and listings in the IDMC report) and through regular data monitoring of the trial.

6.3 Consistency of reporting

Consistency of reporting by centres will be assessed by the IDMC (via tables and listings in the IDMC report) and through regular data monitoring of the trial.

6.4 Missing data

Missing data will be investigated by centre and overall for key variables. Should any patterns emerge then these will be examined. It is expected that the majority of missing data will be at random (except for variables where assessments are not routine done at the centre, e.g. CgA, CgB results) and therefore, it is not expected that imputation methods will be used for individual patients or variables.

7.0 Analysis Methods

7.1 Analysis Populations

Analysis populations will be defined as follows:

- *Intention to treat* (ITT): This population includes all patients enrolled into the study regardless of whether they are later found to be ineligible, a protocol violator, never treated or not evaluated. Patients for whom the primary endpoint cannot be evaluated will be treated as non-responders.

-
- *Evaluable-patient* population: Patients who meet all of the inclusion and exclusion criteria and who start trial treatment are considered evaluable, unless they discontinue treatment prior to 12 weeks for reasons which aren't drug or disease related.
 - *Safety* population: This population includes all enrolled patients who received at least 1 dose of olaparib.

The analysis of the primary outcome will use the evaluable-patient population with sensitivity analyses in the ITT population. All other analyses will use the ITT population. The ITT analysis will treat non-evaluable patients as non-responders. The safety population will be used to characterise the safety profile of olaparib in advanced CRPC patients.

7.2 Baseline Characteristics

Baseline demographics and clinical characteristics will be tabulated overall and by phase/stage of the trial using the ITT population. Numbers (with percentages) for binary, categorical variables and ordered categories plus means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented. Graphical representation will also be used as appropriate.

7.3 Analyses of defined endpoints

7.3.1 Primary endpoint

RECIST response is reported as a category on eCRFs, but individual disease measurements are also provided and these will be used to check the classification (RECIST v1.1 response criteria as outlined in a protocol appendix). Discrepancies will be queried.

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

- Objective response (CR or PR) by modified RECIST or
- Conversion of circulating tumour cell count (CTC) from $\geq 5/7.5$ ml blood at baseline to $< 5/7.5$ ml blood nadir confirmed by a second consecutive value obtained four or more weeks later or
- PSA decline of $\geq 50\%$ (according to the PCWG2)

Response will be evaluated 6 months post registration, however the primary analysis may be conducted prior to this if all patients without 6 months follow up have been evaluated for the primary endpoint or have experienced a treatment failure and discontinued study treatment. The

last value of PSA, CTC count, CT scan and bone scan on or up to four weeks before the date of first study treatment will be used as the baseline value for this assessment. The response rate will be presented along with its exact two-sided 95% confidence interval. For analyses including any patient for whom response has not been confirmed the patient will by default be treated as a non-responder.

7.3.2 Secondary endpoints

The following endpoints will be assessed **6 months post registration**. However, decisions made within the trial to comply with the adaptive design will not necessarily require 6 months follow up on all patients, e.g. it may be possible to enter patients into the second stage of Part A when it is clear between 3 and 14 responses will occur in the first stage even though not all 30 patients have 6 months follow up.

PSA response and **PSA progression** are defined according to the consensus guidelines of the *Prostate Cancer Clinical Trials Working Group 2*:

- PSA partial response is defined as a $\geq 50\%$ decline in PSA value from cycle1 day 1 (baseline). This PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
- PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. The first PSA reading will be obtained at week 12.

Time-to-PSA Progression

For patients who have achieved a $\geq 50\%$ decrease from the cycle 1 day1 (baseline), the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented. This must be confirmed by a second consecutive value obtained 4 or more weeks later. For patients without a PSA decrease of this magnitude or no decrease at all, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented. This must also be confirmed by a second consecutive value 4 or more weeks later. Time to PSA progression will be summarised using Kaplan-Meier methods.

PSA objective response rate (PSA-ORR)

The proportion of patients having achieved partial or complete response defined by PSA will be reported with the corresponding exact two-sided 95% confidence interval.

Pattern of PSA Responses

Waterfall plots will be presented (as per PCWG2 recommendations) that show the percentage of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy), as well as the maximum decline in PSA that occurs at any point after treatment. Waterfall plots provide a broader display of PSA changes than dichotomised responses. Longitudinal plots on mean PSA values along time will also be presented to explore the different patterns of response.

CTC Response

The proportion of patients with a CTC conversion to $<5/7.5$ ml blood at nadir (confirmed by a second consecutive value four or more weeks later) will be presented along an exact two-sided 95% confidence interval. Waterfall plots of CTC falls will also be presented that show the percentage change in CTC counts from baseline to 12 weeks as well as maximal CTC count declines that occur at any point after treatment. Longitudinal plots of mean CTC values across time will also be presented to explore the different patterns of response. Its association with PFS and OS will be examined via landmark analyses (to compare OS or PFS between CTC responders and non-responders at a given time point).

The following endpoints will be evaluated using survival analysis methods (Kaplan-Meier estimation for survival/probability curves):

Radiographic Progression Free Survival (rPFS)

Radiographic progression free survival (rPFS) will be defined by either RECIST progression and /or progression on bone scan (Appendix D and E). It will be measured from the date of trial entry to the first occurrence of radiographic progression or death from any cause. If no event exists, then rPFS will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Time to Radiographic Progression

Time to radiographic progression (progression defined by either RECIST progression and /or progression on bone scan) will be measured from the date of trial entry to the first occurrence of radiographic progression. Death from prostate cancer or any other cause without prior radiographic evidence of progression will not count as an event. If no event exists, then time to

radiographic progression will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Progression Free Survival (PFS)

Progression free survival will be measured from the date of trial entry until radiographic progression, unequivocal clinical progression or death. If no event exists, then PFS will be censored at the last scheduled disease assessment on study or date of death whichever occurs earlier.

Duration of PSA response

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the cycle 1 day 1 (baseline) value (must be confirmed by a second value) until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be censored at the last PSA measurement. Duration of PSA response will be summarised by the median and presented along its 95% confidence interval. Time to PSA response on the duration of response (e.g. by fitting left-truncated models of adjusting by time to response) may be explored.

Duration of response

Duration of response as defined above is calculated from the time response is confirmed until radiographic progression, unequivocal clinical progression or death. If progression free and alive at the end of follow-up, the patient will be censored. Median duration with its 95%CI will be presented. The impact of time to response on the duration of response (e.g. by fitting left-truncated models of adjusting by time to response) may be explored.

Overall Survival (OS)

OS will be measured from the date of trial entry to the date of death (whatever the cause). Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow-up.

7.3.3 Tertiary endpoints

Pain palliation

Pain palliation will be assessed using the Brief Pain Inventory's (BPI Short Form) worst pain intensity score and average score. A composite of the four pain items (worse, least, average, right

now) will be presented as supplemental information. Change in BPI score from baseline will be assessed at 6 months post registration. A reduction of two points in the worst pain score relates to an improvement of pain. The analgesic relief received will be described.

Safety Endpoint

Safety analysis will be summarised using the safety population. Extent of exposure to study drug will be summarised and details will be provided. Treatment emergent adverse events (AEs) are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose. The worst grade from screening or cycle 1 day 1 will be used as the baseline assessment. Adverse events will be graded according to the NCI-CTCAE v4.02. Adverse events will be summarised by grade, according to the worst grade experienced. In addition, most frequently observed AEs will be summarised. In the summary of AE, an AE occurs more than once within a SOC and PT will be counted only once using the worst grade experienced. Serious AE and deaths observed within 30 days of the last dose of study treatment will be provided in a listing.

All adverse events resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of study drug will also be listed and tabulated by preferred term. Clinical laboratory test results will be collected pre-treatment and through 30 days post last dose of study treatment. All laboratory test results will be classified according to the NCI CTCAE v4.02 criteria. Standard reference ranges will be used for missing or discrepant normal ranges. Baseline laboratory test values are the results from the last blood samples drawn on or prior to the first day of study treatment. On-study laboratory test values are those results from blood samples drawn a day after the first study treatment up until 30 days after the last dose of study treatment.

7.4 Treatment compliance

An investigation of treatment compliance of olaparib will involve a summary, either by tabulations or graphically of the following:

- Numbers enrolled
- eligible/ineligible (including reasons)
- discontinuations prior to protocol completion (including reasons)
- doses missed, dose reductions & delays (including reasons)

7.5 Exploratory Analyses

Impact of treatment with olaparib on bone metastases imaging by DW-MRI:

Diffusion-weighted MRI scan will be offered to patients recruited in part A and we expect approximately 50% acceptance rate. This analysis will be purely exploratory and will examine whether response to olaparib expressed by changes in ADCs produced by the DW-MRI scan correlate with 1) PSA decline, 2) CTC conversion and 3) radiological responses coming from conventional imaging. In 20 patients it is possible to detect a correlation coefficient of 0.6 which is equivalent to the parameter explaining 36% of the variation using a 2-sided 5% significance level.

8.0 General Considerations

Progression from Part A to Part B: *Deriving a classifier for identification of tumours with high susceptibility to PARPi olaparib in CRPC.*

All patients participating in this trial will have their archival tissue, fresh tumour biopsies and CTCs collected prior to starting olaparib.

For full details of the biomarker analysis, refer to the Biomarker Statistical Analysis Plan v1.0 (18/02/2015).

8.1 Subgroup analyses

No formal subgroup analyses have been specified.

9.0 Independent Data Monitoring Committee (IDMC) and interim analyses

An Independent Data Monitoring Committee will meet in confidence at regular intervals, firstly to review the safety analysis following the first 5 and 10 patients recruited and subsequently every 6 months (or at intervals determined by them) to review accrual, safety and efficacy data. A report of the findings and recommendations will be produced following each meeting. This report will be submitted to the Trial Management Group and Trial Steering Committee, the main REC and the MHRA, as required.

The replacement of patients who withdraw from the study or who are unevaluable for reasons deemed not to be treatment related will be based on the advice of the committee. The committee will review the results of each interim analysis (progression from stage 1 to stage 2 and progression to part B) and will be asked to advise. These analyses will be supplied in strict confidence by the trial statistician to the IDMC together with any other analyses that the IDMC may request. No results will be made available to investigators or any other party unless the IDMC determines that it would be unethical to withhold the interim results.

The main criterion for early stopping of the trial by the Trial Steering Committee, upon advice from the IDMC and endorsement from the Trial Management Group, will be that evidence from the trial and from other sources suggests a) proof beyond reasonable doubt that for all, or for some types of patient, the treatment regimen is clearly indicated or contra-indicated in terms of response rate and/or toxicity, and b) evidence exists that might reasonably be expected to influence routine clinical practice.

The IDMC will, however, reserve the right to release any data on outcome or side-effects through the Trial Steering Committee to the Trial Management Group (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

10.0 Analysis Programs

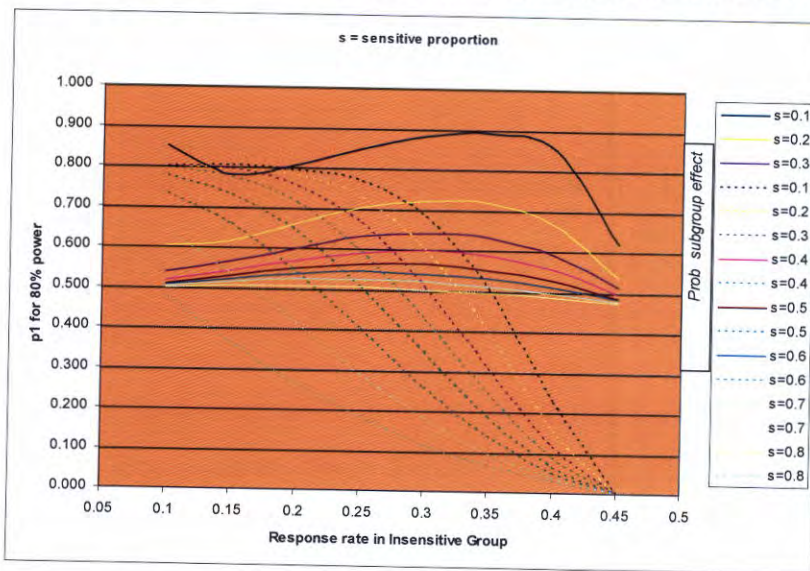
Analysis will be conducted using Stata version 13 (or subsequent versions). Toxicities will be coded according to the latest version of MedDRA available.

11.0 Analysis program locations

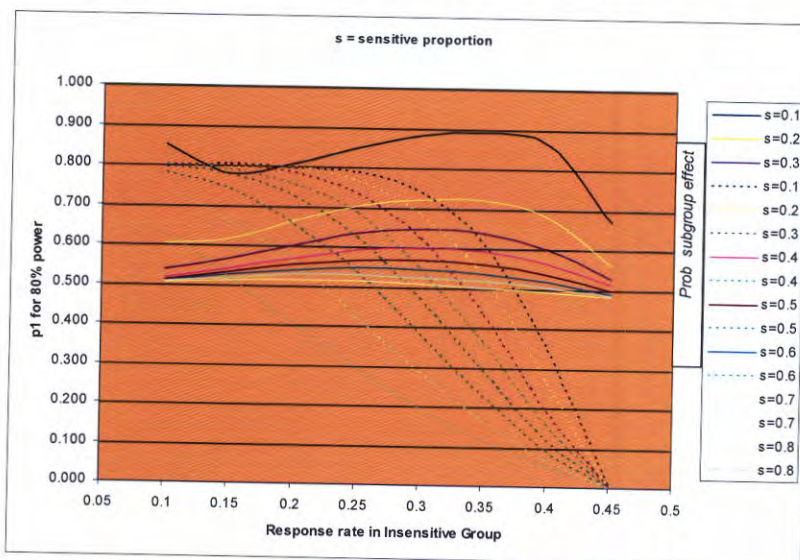
All programs will be stored in the analyses folder for TOPARP (N:\ANALYSES\Toparp) on the ICR-CTSU server. Only the TOPARP trial statistician(s), ICR-CTSU IT staff, Director and Deputy Directors of ICR-CTSU will be able to see the analysis folder. Programmes will be stored under the type of analysis e.g. 'IDMC' or 'Primary analyses'. All official analysis reports that are to be circulated externally of ICR-CTSU will be password protected. Hard copies of reports will be stored securely in the statistical section of the TOPARP trial master file held in a locked fire proof cupboard with restricted access.

Appendix A: Detectable Effects

It is possible to calculate detectable effects in the sensitive group (80% power, y-axis) based on the proportion of sensitive patients (individual lines) and the response rate (x-axis) in the insensitive subgroup. Also shown is the probability a subgroup effect is detected (dashed lines), with 80% power this probability cannot exceed 80%. The fall in the probability of detecting a subgroup effect with increasing response rate in insensitive patients is therefore balanced by an increase in the probability of detecting an overall effect. Thus, in the extreme, if the response rate in insensitive patients is 45% and the response rate in sensitive patients is about 50% a conclusion of overall efficacy will be reached with 80% power, for subgroups of size 30% or more. Using cut offs for Part A of $a_0=15/30$, $a_1=23/45$, as intended.



Using cut offs for Part A of $a_0=18/30$, $a_1=27/45$ the probability of detecting a subgroup effect if the sensitive group is large (>50%) can be improved.



Appendix B: Sample Size Calculations

TOPARP sample size calculations, Part A: alpha 2.2%, Power 90%

Ho : Null Hypothesis Response rate (p0) is 5%

Probability reject **0.97818** alpha 2.2%
 ↑
 Reject first stage 0.81218 (Probability of early termination, sum of values in light blue)
 Reject second stage **0.166** (sum of values in dark blue)

N	po	sum 0.97818													
First	0.05	N second stage													
		0	1	2	3	4	5	6	7	8	15			
0	0.214639														
1	0.338903														
2	0.258637	0.46329	0.3657562	0.13475	0.03073	0.00485	0.00056	4.9E-05	3.3E-06	1.8E-07	3.1E-20			
3	0.12705	0.059	0.046	0.017	0.004	0.001	0	0	0	0		0			
4	0.045136	0.021	0.017	0.006	0.001	0	0	0	0	0		0			
5	0.012353	0.006	0.005	0.002	0	0	0	0	0	0		0			
6	0.002709	0.001	0.001	0	0	0	0	0	0	0		0			
7	0.000489	0	0	0	0	0	0	0	0	0		0			
8	7.4E-05	0	0	0	0	0	0	0	0	0		0			
9	9.52E-06	0	0	0	0	0	0	0	0	0		0			
10	1.05E-06	0	0	0	0	0	0	0	0	0		0			
11	1.01E-07	0	0	0	0	0	0	0	0	0		0			
12	8.39E-09	0	0	0	0	0	0	0	0	0		0			
13	6.11E-10	0	0	0	0	0	0	0	0	0		0			
14	3.91E-11	0	0	0	0	0	0	0	0	0		0			
15	2.19E-12														
16	1.08E-13														
17	4.69E-15														
18	1.78E-16														
.....															
26	3.33E-30														
27	2.59E-32														
28	1.46E-34														
29	5.31E-37														
30	9.31E-40														

Stage I 2.31E-12
 probability of incorrect stopping

H1 : Null Hypothesis Response rate (p1) is 20%

Probability reject **0.10318** Power 89.7%
 ↑
 Reject first stage 0.04418 (Probability of early termination, sum of values in light blue)
 Reject second stage **0.059** (sum of values in dark blue)

N	po	sum 0.10318													
First	0.2	N second stage													
		0	1	2	3	4	5	6	7	8	15			
0	0.001238														
1	0.009285														
2	0.033656	0.03518	0.1319414	0.2309	0.25014	0.1876	0.10318	0.04299	0.01382	0.00345	3.3E-11			
3	0.078532	0.003	0.01	0.018	0.02	0.015	0.008	0.003	0.001	0		0			
4	0.132522	0.005	0.017	0.031	0.033	0.025	0.014	0.006	0.002	0		0			
5	0.172279	0.006	0.023	0.04	0.043	0.032	0.018	0.007	0.002	0.001		0			
6	0.179457	0.006	0.024	0.041	0.045	0.034	0.019	0.008	0.002	0.001		0			
7	0.153821	0.005	0.02	0.036	0.038	0.029	0.016	0.007	0.002	0.001		0			
8	0.110559	0.004	0.015	0.026	0.028	0.021	0.011	0.005	0.002	0		0			
9	0.067564	0.002	0.009	0.016	0.017	0.013	0.007	0.003	0.001	0		0			
10	0.035471	0.001	0.005	0.008	0.009	0.007	0.004	0.002	0	0		0			
11	0.016123	0.001	0.002	0.004	0.004	0.003	0.002	0.001	0	0		0			
12	0.006382	0	0.001	0.001	0.002	0.001	0.001	0	0	0		0			
13	0.002209	0	0	0.001	0.001	0	0	0	0	0		0			
14	0.000671	0	0	0	0	0	0	0	0	0		0			
15	0.000179														
16	4.19E-05														
17	8.63E-06														
18	1.56E-06														
.....															
26	7.53E-15														
27	2.79E-16														
28	7.47E-18														
29	1.29E-19														
30	1.07E-21														

Stage I 0.000231
 probability of incorrect stopping

TOPARP sample size calculations, **Part A**, rule to be applied if no subgroup is found:

Ho : Null Hypothesis Response rate (p0) is 30%

<u>N</u>	<u>p0</u> 0.3	Reject first stage	0.94505 (sum of values in light blue)	alpha	5.5%
0	1.07E-07	16	0.0896266	32	1.3E-08
1	2.06E-06	17	0.0655253	33	2.2E-09
2	1.95E-05	18	0.0436835	34	3.3E-10
3	0.00012	19	0.0266043	35	4.5E-11
4	0.000538	20	0.0148224	36	5.4E-12
5	0.00189	21	0.0075624	37	5.6E-13
6	0.005401	22	0.0035357	38	5E-14
7	0.012895	23	0.0015153	39	3.9E-15
8	0.026251	24	0.0005953	40	2.5E-16
9	0.046252	25	0.0002143	41	1.3E-17
10	0.071361	26	7.065E-05	42	5.3E-19
11	0.09731	27	2.131E-05	43	1.6E-20
12	0.118162	28	5.87E-06	44	3.1E-22
13	0.12855	29	1.475E-06	45	3E-24
14	0.125927	30	3.371E-07		
15	0.111535	31	6.991E-08		

Ha : Alternate Hypothesis Response rate (p1) is 50%

<u>N</u>	<u>p1</u> 0.5	Reject first stage	0.11635	Power	88.4%
0	2.84E-14	16	0.0183782	32	0.00207
1	1.28E-12	17	0.0313511	33	0.00082
2	2.81E-11	18	0.0487684	34	0.00029
3	4.03E-10	19	0.0693024	35	9.1E-05
4	4.23E-09	20	0.0900931	36	2.5E-05
5	3.47E-08	21	0.1072537	37	6.1E-06
6	2.31E-07	22	0.1170041	38	1.3E-06
7	1.29E-06	23	0.1170041	39	2.3E-07
8	6.13E-06	24	0.1072537	40	3.5E-08
9	2.52E-05	25	0.0900931	41	4.2E-09
10	9.07E-05	26	0.0693024	42	4E-10
11	0.000288	27	0.0487684	43	2.8E-11
12	0.000817	28	0.0313511	44	1.3E-12
13	0.002075	29	0.0183782		
14	0.004743	30	0.0098017		
15	0.009802	31	0.0047428		

Table 3 –Co-morbidities and toxicities

Patient ID	Date Randomised	Ongoing Co-Morbidities	Baseline Toxicity	Grade	Cycle 1 Toxicity	Grade	Grades 3/4 at Other Cycles		
							Cycle	Toxicity	Grade
123456	01/01/2013	None	Nausea	1	Nausea Headaches	1 1	-	None	-
...	...								
...									
...									

Table 4 – Concomitant medications that are known to induce xxx

Patient ID	Treatment cycle	Medication
123456	1	Amiodarone
654321	2	Arsenic trioxide
...		

Appendix D: Modified RECIST

The primary efficacy objective to this trial is based on tumour assessment. For the purpose of this study, definitions of soft tissue tumour assessments will be based on a Modified Response Evaluation Criteria in Solid Tumours 1.1 (RECIST1.1). Pertinent points are summarised below.

Evaluation of measurable and non-measurable lesions

1. **Measurable lesions** – lesions that can be accurately measured in at least one dimension with the longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm, with a spiral CT scan.
2. **Non-measurable lesions** – all other lesions, including small lesions (longest diameter ≤ 10 mm, with a spiral CT scan), i.e., blastic bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
3. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, should not be included in assessment of response, but should be assessed for progression.
4. For this study, bone lesions are not considered “non-measurable” lesions for RECIST. Bone lesions will be assessed by bone scan only.
5. All measurements should be taken and recorded in metric notation, using a ruler or calipers. Preferably, all screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.
6. The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up.
7. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion is recommended.

Methods of measurement:

1. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.
2. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung, however CT scans are preferable.

3. Ultrasound (US), endoscopy and laparoscopy should not be used to measure tumour lesions. It is however a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound may also be used to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
4. Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions).

Baseline documentation of target and non-target lesions

1. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline and at the time points specified in the protocol.
2. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements.
3. A sum of the longest diameters (LD) for all target lesions will be calculated and reported as the baseline sum of LD. The baseline sum LD will be used as reference by which to characterise the objective tumour response.
4. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions will also be monitored throughout the study, and an overall assessment of response will be made. Details of any new lesions will also be recorded. It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Table 9: Response Criteria

Response criteria	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD)	At least 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	Whether sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Table 10: Responses in patients with both target and non-target disease

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/nonPD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD= progressive disease, NE= inevaluable

Table 11: Responses in patients with only non-target disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/nonPD	No	Non-CR/nonPD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD= progressive disease, NE= inevaluable

Reproduced from: <http://www.recist.com/recist-comparative/01.html> and Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 12 weeks) that is defined in the study protocol.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

Appendix E: Bone metastases evaluation

The first bone scan should not be performed before 12 weeks post commencement of treatment unless clinically indicated as there may be evidence of a flare response early on which may confuse the response evaluation. A patient will be considered to have progressed on bone scan if the following criteria are met:

- If the first bone scan with 2 new lesions is observed ≤ 13 weeks from the point of Cycle 1 Day 1 and is confirmed by a follow up scan ≥ 6 weeks later showing 2 additional new lesions (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan).
- The first bone scan with ≥ 2 new lesions compared with baseline is observed > 13 weeks from Cycle 1 Day 1 and the new lesions are verified on the next bone scan ≥ 6 weeks later (i.e. a total of ≥ 2 new lesions compared with baseline). If the second scan confirms progression the data of the progression is the date of the first bone scan rather than the second confirmatory scan.

Measurable Disease Evaluation:

Changes in nodal and visceral disease should be recorded using the modified RECIST criteria defined in Appendix E.

Table 8: Radiological Criteria for Ascribing Disease Progression

Evidence of Progression	Confirmation	Action
Bone Disease Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment ≤ 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show an additional 2 new lesions compared to the first post treatment scan (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment > 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should confirm the presence of the 2 new lesions compared the baseline scan. (i.e. a total of ≥ 2 new	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.

	lesions compared with the baseline bone scan).	
Soft Tissue Disease as defined by RECIST on CT/MRI	Progression at any scheduled reassessment \geq 12 weeks does not need to be confirmed.	Investigators are highly encouraged to maintain the patient's treatment with study medication unless radiological progression is observed.

TOPARP

Phase II Trial of Olaparib in Patients with Advanced
Castration Resistant Prostate Cancer

Statistical Analysis Plan [Part A biomarker analysis]

Version 1.0

18/02/2015

This statistical analysis plan is based on protocol version 4.0 [15/04/2014]

ISRCTN Number: 15124653

REC reference number: 11/LO/2019

CR UK (other funder) number:

CRUK/C12540/A12354

EUDRACT number: 2011-000601-49

ICR-CTSU Number: ICR-CTSU/2011/10030

CTA reference number: 22138/0016/001-
0001

Sponsor reference number: 3592

The current draft version of SAP if prior to principal analysis of primary endpoint, any previous draft versions used for formal presentation, i.e. peer reviewed conference posters/presentations prior to the principal analysis, and any final version(s) of the SAP will be stored in the Statistical Section of the Trial Master File

This statistical analysis plan is a framework to guide statistical analysis and may be supplemented by additional and exploratory analyses. Trial statisticians reserve the right to amend analysis methods as appropriate after discussion with the ICR-CTSU Scientific Lead.

For final versions only:

This statistical analysis plan has been approved by the following personnel:

Trial Statistician: Helen Mossop, Nuria Porta

Signed: H. Mossop

Date: 11/3/15

ICR-CTSU Scientific Lead: Emma Hall

Signed: Emma Hall

Date: 11/3/15

Chief Investigator: Johann de Bono

Signed: Johann de Bono

Date: 28/3/2015

Document history

Version	Date	Changes made
0.1	18/12/14	First draft based on Template v3 ST.02.G1.F1 and draft of Statistical Analysis of Part A Biomarker Selection Methods for IDMC_v1
1.0	18/02/2015	Update to definition of evaluable patient population as per main SAP. Update to BRCAness definition

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1.0 Introduction

This statistical analysis plan provides guidelines on the biomarker-related analysis and publication of Part A patients. The design and statistical analysis of Part A clinical data have been described in the TOPARP Statistical Analysis Plan v2.0 (18/02/2015).

With the purpose of submitting biomarker analysis results to AACR (deadline 27/02/2015) and for opening Part B of the trial, an analysis to identify predictive biomarkers of response will take place when response data at 6 months for all Part A evaluable patients is available. The principal (main) analysis of Part A to be included in the primary publication of Part A will take place at a later date, following thorough data cleaning, central review of scans and to allow survival data to mature..

This SAP will be used to guide the biomarker analysis and to minimise bias due to data-driven choices of analysis. Any deviations from the analysis plan will be documented in the Statistical Analysis Report. Details of efficacy and safety analyses are given in the main TOPARP SAP and are not reproduced here where unnecessary. Details of data monitoring are stored in the Central Statistical Monitoring Plan and are not reproduced here.

1.1 Trial design

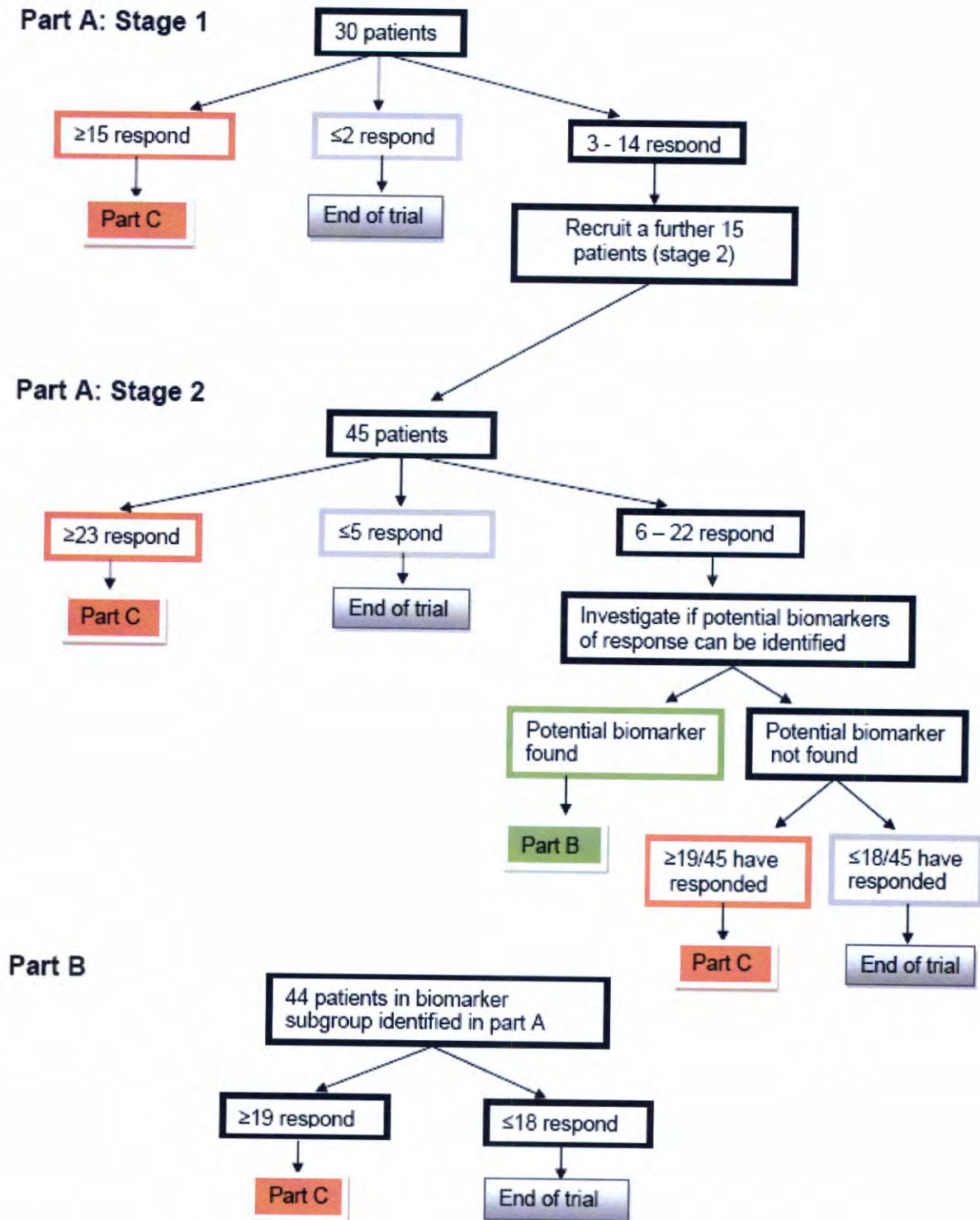
TOPARP is a single arm, multi-centre, open label, two-stage phase II clinical trial addressing the hypothesis that olaparib will improve the response for patients with advanced CRPC who have failed androgen deprivation and taxane-based treatment.

The study is divided into 2 parts. Part A is an efficacy screening stage for sensitive biomarkers. It is designed as an open-labelled, non-randomised two-stage design both to allow the activity of olaparib in unselected advanced CRPC patients to be evaluated, and to permit the development of predictive biomarkers of response to olaparib. Part B is a subsequent 'validation' or 'confirmation' stage, which will be undertaken if confirmation of activity in a biomarker defined subgroup is necessary. It is an open-labelled, single stage assessment of anti-tumour activity of olaparib in preselected patients based on putative biomarkers of PARP inhibitor sensitivity and DNA repair deficiency previously identified in Part A. At least 89 evaluable patients will be enrolled to Parts A & B.

Patients will be administered oral olaparib tablets, 400mg BID continuously until disease progression is documented and confirmed (i.e. confirmed radiographic progression) or withdrawal for another reason.

Refer to TOPARP Statistical Analysis Plan v2 (18/02/2015) for further details.

Figure 1: Overview of the main TOPARP trial design



Part C will only be initiated if the anti-tumour activity observed in Parts A and B are sufficient to warrant a randomised study. The design of Part C will be determined following the analysis of Parts A/B.

2.0 Biomarker analysis objectives

The aim of this design is to look for potentially sensitive subgroups of patients by undertaking a screening trial (part A) followed by a validation trial (part B) if there is evidence a sensitive subgroup exists.

The aim is to identify a sensitive subgroup with a 50% response rate on the basis that high response rates are necessary to be confident of demonstrating longer-term progression-free or survival benefits.

3.0 Biomarker data

3.1 Immunohistochemical and Sequencing data:

All patients participating in TOPARP Part A will have archival tissue and fresh tumour biopsies collected prior to starting olaparib available for central laboratory analysis. DNA will be extracted from the tissues, subject to whole exome sequencing (WES) and targeted sequencing of specific genes will be performed on frozen biopsy tissues collected at pre-treatment. The list of genes included in the targeted sequencing, will be selected by the central laboratory team under the direction of the TOPARP Chief Investigator and is based on evidence from existing literature as well as those identified from the WES on the TOPARP materials. Immunohistochemical assays will be used to detect biomarker antigens expression.

The selection of genes to be related to clinical outcome data will be based on a pre-defined algorithm, as summarised in Appendix A, independent of knowledge of clinical response data.

Data from all chosen genes will be provided to the trial statisticians in dichotomous format; present or not present.

Each tumour tissue will have molecular characteristics classified based on the following biomarker:

1. PTEN loss by immunohistochemistry (IHC)
2. ERG gene rearrangement by IHC
3. BRCAness
 - a. ATM expression
 - b. BRCA1/2 deficiency status
 - c. Other biomarkers identified to sensitize to PARP inhibitors

PTEN loss will be assessed as a dichotomous variable, defined as negative if scored between 0-10 and positive if scored >10 on IHC.

ERG expression will be assessed as a dichotomous variable, defined as positive if any ERG protein expression is present on staining and negative if no ERG protein expression is present on staining.

BRCAness will be identified as a subgroup of patients with phenotypes displaying traits that are shared with those occurring in either BRCA1 or BRCA2-mutation carriers ⁽¹⁾. Patients presenting with a multiple biomarkers signature for BRCAness will be referred to as positive and negative. ATM expression will be dichotomous; negative or positive. BRCA1 and BRCA2 mutation testing will be dichotomous defined as mutated or normal.

3.2 Pharmacodynamics markers

The following genes will be assessed using Immunofluorescence (IF) on pre and post dose fresh tissue biopsies:

1. **RAD51**
2. γ H2AX
3. 53BP1 IF
4. Geminin

Note that there is emerging evidence to suggest that RAD51 foci formation is diminished in tumours with homologous recombination (HR) defects such as those with loss of PTEN and ETS rearrangements.

As well assessing predictive ability using the baseline score, changes from baseline will also be explored.

Data received will be continuous, representing the percentage of cells on IF expressing/not expressing each biomarker. Cut offs for categorising a cell as positive will be pre-specified using evidence from current literature at the time of the analysis.

4.0 Primary efficacy endpoint

Biomarker data will be related to clinical response data. Response is defined as follows:

- *Response:*

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

 - Objective response by modified RECIST (baseline lymph node size must be ≥ 2 cm to be considered a target lesion) or
 - Conversion of circulating tumour cell count (CTC) from $\geq 5/7.5$ ml blood at baseline to $< 5/7.5$ ml blood nadir confirmed by a second consecutive value obtained four or more weeks later or
 - PSA decline of $\geq 50\%$ (according to the PCWG2)

Evaluable patients with no confirmed response as defined above will be classified as non-responders.

5.0 Data completeness and consistency

As part of the principal analysis of the biomarker analysis for publication a CONSORT diagram will be provided. This will include the number of patients with sample data available, and usable, for the biomarker analysis and patients with efficacy data available. The reasons for unusable sample data will be provided. The number of patients who discontinued with trial treatment and reasons for discontinuation will also be provided.

5.1 Data cleaning

Any inconsistent or abnormal biological data will be queried with the laboratory team.

6.0 Analysis methods

6.1 Analysis populations

Analysis populations will be defined as follows:

- *Biological study* population: This population includes all patients who have baseline biopsy samples available and evaluable for the primary biomarkers of interest. Patients may have to be excluded from analyses for practical reasons such as assay failures, insufficient DNA.
- *Evaluable-patient* population: Patients who meet all of the inclusion and exclusion criteria and who start trial treatment are considered evaluable, unless they discontinue treatment prior to 12 weeks for reasons which aren't drug or disease related. Where evaluability is difficult to define the final decision will rest with the IDMC. This population is as for clinical analyses conducted under TOPARP Statistical Analysis Plan v2 (18/02/2015).
- *Biological evaluable-patient* population: This population contains all evaluable patients, as defined above, and have data available for the primary biomarkers of interest.

6.2 Baseline characteristics

Baseline demographics and clinical characteristics will be tabulated overall and by phase/stage of the trial using the evaluable patient population and will be summarised in evaluable patients with and without availability of biological data. Numbers (with percentages) for binary, categorical variables and ordered categories plus means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented. Graphical representation will also be used as appropriate.

6.3 Primary analysis

The choice of biomarker(s) to be investigated further in Part B will be based on the predicted probability of success in Part B given the responses observed in Part A.

Biomarkers with a predictive probability of success of 60% or more in Part B will be chosen, this corresponds approximately to a 50% or more response rate in the predefined subgroup. Appendix B summarises the probability of taking a subgroup into part B, given its true response rate, response rate in the biomarker negative subgroup and the biomarker subgroup size.

The biomarker data will be associated with response data using a multivariable logistic regression model, with the choice of predictive variables to retain in the model chosen using backward elimination. Standard prognostic factors may be included in the classifier if they are independent of the biomarkers. Prognostic factors may include, but are not limited to:

- LDH (\leq Upper Limit of Normal (ULN)* / $>$ ULN)
- ECOG PS (0-1 / 2+)
- Haemoglobin (continuous)
- Alkaline Phosphatase (\leq ULN* / $>$ ULN)
- Albumin (Continuous)
- Presence of visceral metastases (Yes – incl. liver / Yes – excluding liver / No)
- Baseline CTC count (explored as both continuous and $\leq 50/7.5$ ml blood / $> 50/7.5$ ml blood)

*Note that ULN will be site dependent.

Interactions between the biomarker variables, and with prognostic factors if necessary, will be explored and considered in the model.

The final goal of the aforementioned model building exercise is to develop a classifier which identifies a group with a response rate of 40% or more on the basis that the levels for inefficacy and efficacy are set at 30% and 50% respectively.

6.4 Exploratory analysis

If evidence exists from other sources it may be incorporated into the assessment of specific biomarkers using either or both following approaches:

(a) Bayesian methods, i.e. a prior distribution will be defined such as stating the true effect is liable to lie between 35% and 65% based on external evidence

(b) performing meta-analysis including results from other reports to give an 'overall' p-value or using

Biomarkers for which there is very strong external evidence will be taken into Part B irrespective of results in Part A.

If dynamic biomarker data are available, the appearance of foci for RAD51, Geminin, γ H2AX, 53BP1 IF will be assessed on both pre and post dose biopsies. Relative changes from baseline will be explored to assess the effect of alterations in DNA repair.

Change from baseline will be defined as the $\log(\text{post-dose/pre-dose score})$. The change in each variable will be associated with response data using a multivariable logistic regression model. Standard prognostic factors may be included if they are independent of the biomarkers.

7.0 General considerations

- A significance level 10% will be used for selecting variables to retain in the logistic regression model.
- Backward elimination performed using the stepwise command in Stata.

8.0 Subgroup analyses

No formal subgroup analyses for identifying predictive biomarkers of response to olaparib have been specified.

9.0 Analysis Programs

Analysis will be conducted using Stata version 13 (or subsequent versions).

10.0 Analysis program locations

All programs will be stored in the analyses folder for TOPARP on the ICR-CTSU server. Only the TOPARP trial statistician(s), ICR-CTSU IT staff, Director and Deputy Directors of ICR-CTSU will be able to see the analysis folder. Programmes will be stored under the type of analysis e.g. IDMC meeting. All official analysis reports that are to be circulated externally of ICR-CTSU will be password protected. Hard copies of reports will be stored securely in the statistical section of the TOPARP trial master file held in a locked fire proof cupboard with restricted access.

Appendix B – probability of taking a subgroup into Part B

The table below shows the probability a biomarker will go into Part B given its true response rate (p_1), the response rate in other patients (p_0) and the proportion of patients in the ‘sensitive’ biomarker subgroup (subgroup size).

As an example, there is a 57.2% chance that marker X will go through Part B if in insensitive patients we observe a response of 30% whilst in the sensitive subgroup (10% subgroup size) we observe a response of 50%.

Examples of response rates that would warrant taking a biomarker into Part B are (responders/total) 3+/5, 5+/10, 7+/15 , 10+/20, 12+/25.

Probability of taking sensitive subgroup into part B (%) ~ power

Response Rate in insensitive patients	p_1	'Sensitive' Subgroup Response Rate (%)				
		Subgroup Size (%)				
		10	20	30	50	70
$p_0=30\%$	30	26.8	14.2	10.6	6.1	4.9
	40	42.8	33.0	34.7	27.8	28.1
	50	57.2	57.6	64.3	65.9	72.2
	55	62.9	68.8	75.4	81.7	87.2
	60	73.5	79.2	85.5	91.0	95.0
	70	86.6	93.0	95.5	99.1	99.9
$p_0=25\%$	30	25.3	15.3	10.5	6.8	4.4
	40	42.9	34.1	34.2	27.8	29.1
	50	59.9	58.9	62.1	67.4	72.1
	55	68.0	71.3	74.8	82.6	88.1
	60	73.6	77.6	84.3	91.1	95.7
	70	85.5	92.6	96.3	99.5	100.0
$p_0=20\%$	30	26.8	13.7	13.9	6.9	4.5
	40	43.9	34.5	34.2	32.2	30.6
	50	59.4	56.6	62.1	68.9	75.4
	55	66.8	69.4	74.4	84.0	87.6
	60	74.0	80.3	85.3	92.3	95.5
	70	87.2	91.5	96.0	99.3	99.7

Probability that Part B will be undertaken

The next table shows the probability PART B will be undertaken under the same scenarios as above.

In the above example we noted that there is a 57.2% chance that marker X will go through Part B if in insensitive patients we observe a response of 30% whilst in the sensitive subgroup (10% subgroup size) we observe a response of 50%. The table below shows that there is a 67.1-57.2= 9.9% chance another subgroup will be wrongly selected to go into PART B.

<u>Response Rate in insensitive patients</u>		<u>Probability Part B will be undertaken (%)</u>				
		<u>'Sensitive' Subgroup Response Rate (%)</u>	<u>Subgroup Size (%)</u>			
			<u>p₁</u>	<u>10</u>	<u>20</u>	<u>30</u>
p ₀ =30%	30	40.9	33.5	29.6	23.7	24.6
	40	55.5	45.6	50.2	46.1	51.7
	50	67.1	67.2	74.5	78.0	84.3
	55	71.5	75.6	81.8	88.6	92.9
	60	79.1	84.7	89.2	94.1	97.2
	70	90.5	94.5	96.9	99.5	100.0
p ₀ =25%	30	31.8	23.8	20.2	19.5	21.3
	40	49.2	43.4	45.4	43.1	50.4
	50	64.2	64.4	68.6	74.4	82.7
	55	71.4	76.1	79.2	87.3	93.2
	60	76.3	81.3	87.3	94.1	98.0
	70	86.6	93.6	97.4	99.7	100.0
p ₀ =20%	30	28.8	18.7	19.0	14.8	17.2
	40	44.8	39.3	40.6	42.5	46.1
	50	60.0	60.1	65.4	75.2	81.8
	55	67.3	71.8	76.8	86.6	92.6
	60	74.1	81.1	87.4	93.5	96.7
	70	86.6	91.8	96.8	99.5	99.7

A fundamental aim of TO-PARP is that biomarkers with a response rate of 50% or more have a high probability of being selected for study in Part B, this is largely true.

