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Targeting Resistant Prostate Cancer With ATR and PARP Inhibition (TRAP Trial)

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A Multi-Center Phase II Study Testing the Activity of Olaparib and AZD6738 (ATR Inhibitor) in Metastatic Castration-Resistant Prostate Cancer.

Short Title: Targeting Resistant prostate cancer with ATR and PARP inhibition (TRAP trial)

PROTOCOL SYNOPSIS

A Multi-Center Phase II Study Testing the Activity of Olaparib and AZD6738 (ATR Inhibitor) in Metastatic Castration-Resistant Prostate Cancer.

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Study site(s) and number of subjects planned

The study will enroll 47 evaluable patients from 4 academic centers.

Study period	Phase of development
Estimated date of first subject enrolled	1/2019
Estimated date of last subject completed	4/2021

Study design

This is a phase II Simon 2-stage study evaluating the response rate for the combination of AZD6738 (ceralasertib) and olaparib for patients with metastatic castration-resistant prostate cancer (mCRPC) who are DNA repair proficient (DRPro) and deficient (DRDef). Patients are DRDef based on somatic mono- or bi-allelic loss of ATM, somatic biallelic loss of either BRCA1 or BRCA2 OR known mono- or biallelic germline loss in ATM, BRCA1 or BRCA2.

Objectives

Primary Objectives:	Outcome Measures:
To determine the response rate of the combination of olaparib and AZD6738 in mCRPC patients who are DNA repair proficient (DRPro, e.g. intact ATM, BRCA1 and BRCA2).	The rate of response (CR/PR) per radiographic response according to RECIST v1.1 or PSA (≥50% decline) in DRPro patients.

Secondary Objective:	Outcome Measure:
To determine the response rate of the combination of olaparib and AZD6738 in mCRPC patients who are DNA repair deficient (mono- or biallelic somatic ATM loss or biallelic somatic loss of BRCA1 or BRCA2 OR known mono- or biallelic germline loss of ATM, BRCA1, or BRCA2).	The rate of response (CR/PR) per radiographic response according to RECIST v1.1 or PSA (≥50% decline) in DRDef patients.
All of the below secondary objectives will be calculated for the DRPro, DRDef patients separately.	
Objective progression-free survival (combined radiographic and clinical progression-free survival)	The objective progression-free survival is the duration of time from start of treatment to date of progression (based only on radiographic progression or clinical decline/death).
Objective radiographic disease response rate	The rate of achieving a radiographic response according to RECIST v1.1.
PSA progression-free survival	Composite of survival and duration of PSA control as defined by time from start of therapy to first PSA increase ≥ 25% and ≥2 ng/ml above the nadir and confirmed by a second value at or beyond 4 weeks later.

PSA response rate for ≤ 0.2 ng/ml, 50% decline, 90% decline from entry PSA and confirmed 4 weeks later	The rate of achieving the aforementioned PSA value or percent decline compared to PSA at entry.
Duration of combined radiographic and PSA response	Time from first documented response (RECIST v1.1 CR/PR or PSA decline ≥50%) until death, recurrent or progressive disease (based on RECIST v1.1) or first PSA increase ≥ 25% and ≥2 ng/ml above the PSA nadir.

Safety Objective:	**Outcome Measure:**
To evaluate the quantitative and qualitative tolerability of the combination within the combined, DRPro and DRDef patients.	AE summaries and treatment exposure by genetic subtype

Exploratory Objective:	**Outcome Measure:**
To evaluate the predictive capacity of circulating analytes within both genetic cohorts.	Circulating tumor DNA sequencing/quantification, circulating tumor cell number, circulating tumor cell composite gene expression by pooled RT-PCR.

Target subject population

Patients with progressive, metastatic, castration-resistant prostate cancer who received a) at least one line of systemic therapy for mCRPC or b) failed ongoing second generation anti-hormonal therapy (e.g. abiraterone) in the hormone-sensitive or non-metastatic castration resistant phases of disease. They must remain on continuous LHRH agonist/antagonist, unless they have undergone orchiectomy.

Duration of treatment

Patients must have washed out of any prior systemic therapy for either 3 weeks or 5 half-lives (whichever is longest), excluding prednisone, LHRH agonist/antagonists, bisphosphonate or RANKL inhibitor. The median duration of study per patient is estimated to be approximately 12 months.

Investigational product, dosage and mode of administration

Olaparib, 300 mg by mouth, twice a day, days 1-28 of a 28-day cycle.
AZD6738, 160 mg by mouth, daily, days 1-7 of a 28-day cycle.

Statistical methods

For the DRPro population (characterized through study sequencing or previously completed), using an Optimal Simon 2-stage design, this cohort will be 35 total patients with an interim for futility after 17 DRPro patients have been accrued. If 2 or more responses are seen in the first stage, then the second stage will open and accrue 18 more DRPro patients. If 5 or more patient responses are seen out of the 35 DRPro patients, then the combination treatment will be deemed interesting for further study in a DRPro population. The null response rate from the

TOPARP-A study is 6%. The current design will detect at 80% power, a response rate of 20% or greater with 5% one-sided type I error.

For the DRDef population (characterized through study sequencing or previously completed), using a Mini-Max Simon 2-stage design. A set of 12 DRDef will be treated and if 6 or more responses are seen, this would support consideration to expand (with amendment or new protocol) with another 13 patients or a completely separate trial.

Principal analyses will report the response rate (CR/PR) per radiographic response according to RECIST v1.1 or PSA (≥50% decline) in DRPro and DRDef patients. The cohorts will be separated for all efficacy analyses.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or Special Term	Explanation
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
APTT	Activated Partial Thromboplastin Time
AR	Androgen Receptor
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATM	Mutated in Ataxia Telangiectasia
ATR	Ataxia telangiectasia and Rad3-related protein
AUC	Area Under the Curve
BID	Twice a Day
BRCA1	Breast Cancer 1 Gene
BRCA2	Breast Cancer 2 Gene
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CHK1	Checkpoint Kinase 1
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum Concentration
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form (electronic/paper)
CRPC	Castration-Resistant Prostate Cancer
CT	Computed Tomography
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating Tumor DNA
CYP	Cytochrome P
DNA	Deoxyribonucleic acid
DRPro	DNA repair defect negative
DRDef	DNA repair defect positive
DSMC	Data and Safety Monitoring Committee
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ESMO	European Society of Medical Oncology
FDA	Federal Drug Administration
FU	Follow up
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
γH2AX	Gamma-Histone 2AX
Hb	Hemoglobin
HDPE	High-density Polyethylene
ICH	International Conference on Harmonisation
IND	Investigational new Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IV or iv	Intravenously
LDH	Lactate Dehydrogenase
LHRH	Luteinizing Hormone Releasing Hormone
mCRPC	Metastatic Castration-Resistant Prostate Cancer
mHSPC	Metastatic Hormone-Sensitive Prostate Cancer
MDS	Myelodysplastic Syndrome
MIAP	Michigan IND/IDE Assistance Program
MRI	Magnetic Resonance Imaging
MSPM	Multi-Site Project Manager
NCCN	National Comprehensive Cancer network
NCI	National Cancer Institute
OATP1B1	Organic Anion Transporting Polypeptide 1B1
PARP	Poly (ADP-Ribose) Polymerase
PCWG	Prostate Cancer Working Group 3
PD	Progressive Disease
PE	Physical Exam
PFS	Progression Free Survival
Pgp	P-glycoprotein
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial Response
PSA	Prostate Specific Antigen
PT	Prothrombin Time

RANKL	Receptor activator of nuclear factor kappa-B ligand
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic Acid
SAE	Serious adverse event
SOP	Standard Operating Procedures
ULN	Upper Limit of Normal
URI	Upper Respiratory Infection
WBC	White Blood Cells

1. INTRODUCTION

1.1 Background

In 2017, approximately 26,000 men are estimated to have died from prostate cancer in the United States, making it the third leading cause of cancer death in men [1]. Prostate cancer is an androgen driven disease, yielding a high initial response rate to androgen deprivation therapy (ADT) in the metastatic setting. Despite survival advances through the addition of docetaxel chemotherapy or abiraterone (testosterone biosynthesis inhibitor) to ADT in this hormone-sensitive phase of disease, many men will have their disease progress despite the low testosterone environment. This is termed metastatic castration-resistant prostate cancer (mCRPC). Multiple therapy options exist and include further androgen targeting therapies (abiraterone, enzalutamide), immunotherapy (sipuleucel-T), bone directed therapies (Radium-223, bisphosphonates, RANKL inhibitor) and chemotherapies (docetaxel, cabazitaxel). These drugs often improve oncologic symptoms, yet the median survival gains of each remains around 3 months. The need for new options remains great.

Precision oncology (matching tumor specific genetic changes to drugs targeting those alterations/pathways) is revolutionizing cancer care. Preliminary results have shown this strategy may be effective in prostate cancer by targeting DNA repair pathways. Approximately 20% of mCRPC patients have germline or somatic loss of DNA repair genes (dominated by BRCA2, ATM) rendering them DNA repair deficient (DRDef) [2]. Targeting this DRDef population with poly (ADP-ribose) polymerase (PARP) inhibitors has shown promise in two phase II studies. The first was an unselected trial where DRDef patients were uniquely sensitive to olaparib (a PARP inhibitor) resulting in an 88% response rate (based on CTC number, radiographic and PSA effects). DNA repair defect negative (DRPro) patients had only a 6% response rate [3]. A separate trial suggests activity, but wasn't designed or powered towards that hypothesis. When treated with abiraterone, prednisone and veliparib (a PARP inhibitor), 12 of 13 (92.3%) DRDef patients had a PSA decline of >50% and 10 of 11 (90.9%) DRDef patients with measurable disease had a RECIST response. This compares favorably to DRPro patients who had a 64.7% PSA response rate and 40% RECIST response to the same combination [4]. Finally, retrospective analysis of excellent responder patients treated with platinum agents (cisplatin or carboplatin) also found them to be DRDef (BRCA2 carriers), further supporting targeting DNA repair in this population. [5].

The problem remains, that only 20% of mCRPC patients are DRDef. To simulate this genomic requirement, combinations of DNA repair targeting agents have been attempted. Cisplatin and cisplatin/gemcitabine were combined with olaparib but hematologic toxicity was limiting [6, 7]. Carboplatin and carboplatin/paclitaxel were combined with a PARP inhibitor (rucaparib or olaparib) with a better tolerability profile, but unknown benefit [8, 9]. Various carboplatin combinations remain in clinical study. Although small in number, responses seen in these early clinical trials remain in DRDef patients. The 80% DRPro patients in prostate cancer remain without a proven DNA targeting regimen.

Ataxia telangiectasia and Rad3-related protein (ATR) is an attractive DNA repair target candidate due to its involvement in cell cycle checkpoint regulation, stalled replication fork resolution, single strand break repair (with Replication Protein A) and double strand break

repair (with ATR Interacting Protein). With the high prevalence of prostate cancer and known role for DNA repair targeting, it is an ideal scenario to test ab ATR/PARP inhibitory combination.

1.1.1 **Pre-clinical experience**

AZD6738 is a potent inhibitor of the ATP-kinase domain of ATR with a purified target IC_{50} of 1 nM. Its closest off-target *in vitro* kinase inhibition is mammalian Target of Rapamycin (mTOR) at 370 nM, while the majority of kinases are in the µM range. Selectivity remains in cellular assays. Mechanistic validation was done by monitoring the decline of phosphorylated CHK1 (ATR's target in cell-cycle regulation) and rise in γH2AX (marker of double stranded DNA repair) with increasing doses of AZD6738 by western blot. Exposure to AZD6738 also causes S-phase arrest due to extensive DNA damage by flow cytometry. Cell-lines with deficient ATM function showed a 5x lower GI_{50} concentration. To overcome this genetic requirement, AZD6738 was combined with multiple chemotherapies. Focusing on the olaparib combination, this resulted in synergistic activity for 50% of tested cell lines, while only additive for the remaining. Of note, none showed reduced efficacy in combination. Cell lines with lower ATM expression had higher synergy scores, suggesting DRDef cancers respond stronger to the combination, yet DRPro lines remained additive.

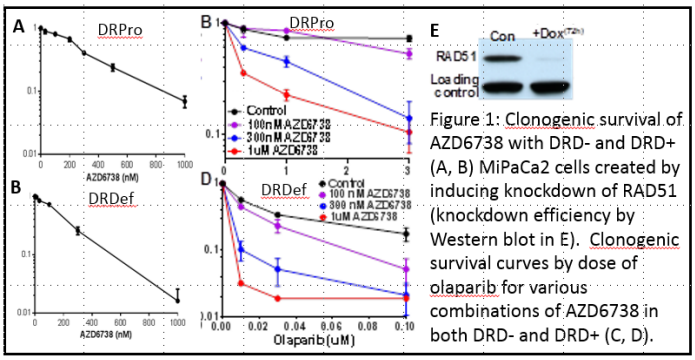


Figure 1: Clonogenic survival of AZD6738 with DRD- and DRD+ (A, B) MiPaCa2 cells created by inducing knockdown of RAD51 (knockdown efficiency by Western blot in E). Clonogenic survival curves by dose of olaparib for various combinations of AZD6738 in both DRD- and DRD+ (C, D).

To further genetically narrow the DNA repair proficiency vs deficiency argument, MiaPaCa2 cells with a stable doxycycline-inducible RAD51 shRNA knockdown (resulting in a DRDef signature), were tested with and without doxycycline. AZD6738 resulted in decreased clonogenic survival as monotherapy for both DRDef and DRPro lines. The combination also showed improved effects at lower doses of AZD6738 with olaparib (Figure 1).

The combination of AZD6738 and olaparib has also been tested *in vivo* in several triple-negative DRDef breast cancers xenograft models with similar effect. A mutated ATM line resulted in 100% growth inhibition for the combination, with only 30% (AZD6738) or 0% (olaparib) growth inhibition for monotherapy. Two BRCA2 deficient lines also had exquisite sensitivity to the doublet with variable monotherapy results.

1.1.2 **Toxicology and safety pharmacology summary**

AZD6738 and olaparib are cleared via CYP3A4. Adverse events of AZD6738 in dogs, guinea pigs or rats resulted in weight loss, decreased food consumption, bone marrow suppression (all lines), biliary epithelial degeneration, degenerative changes in male reproductive tissues, hypotension, tachycardia, delayed gastric emptying, vomiting, or diarrhea. AZD6738 was not mutagenic in the Ames test, but was positive in the in *vitro* mouse lymphoma assay and *in vitro* micronucleus assay in human lymphocytes consistent with its known DNA repair inhibition.

Bone marrow suppression typically manifested as neutropenia and/or thrombocytopenia, which were the main dose limiting toxicities. Improved regimens consisting of a 7-day AZD6738 and 28-day olaparib exposure with dose reductions, delays and supportive care (e.g. transfusions) mitigated many side effects. Upon drug discontinuation, no persistent effects were noted. Grade 3-4 toxicities observed in one or more patients include anemia, ascites, anorexia, abdominal pain, intestinal obstruction leukopenia, dehydration and syncope. Other less severe side effects include fatigue, nausea, vomiting, dizziness, diarrhea, asthenia and blood creatinine increase.

1.1.3 **Clinical experience**

There is extensive clinical data regarding olaparib monotherapy with its approval and use in ovarian and breast cancer [10-12]. AZD6738 is in phase 2 development and has been combined with olaparib in dose-finding studies, with expansions in gastric cancer and breast cancer are ongoing. Within the phase I study of the combination, 6 patients (15%) had a confirmed RECIST complete or partial response and each was DRDef. Due to the variable doses exposed, and low percentage of prostate cancer patients within the phase I trial (<10%), a prostate cancer specific trial is presented.

1.2 Research Hypothesis

This is an open label, single arm study design, with two subspecified genetic cohorts: DRPro and DRDef patients. Each cohort is separated in the statistical analysis for efficacy but combined for tolerability. The rationale for drug efficacy for both cohorts is covered in Section 1.1. The historical data discussed in Section 1.1 describes the futility of single agent DNA repair targeting in DRPro disease, such that the focus is on evaluating activity of the combination.

To define the cohorts, patients with previous mCRPC or mHSPC metastatic tissue based tumoral testing and those with known germline BRCA2, BRCA1 or ATM loss will not require a new biopsy. Patients with an unknown tumor status will undergo a metastatic site biopsy to evaluate DNA repair status. If a biopsy is unable to be done because of procedural risk or a biopsy is attempted and yields insufficient tissue, patients may (if available) undergo circulating tumor DNA testing (e.g. Tempus) for exploratory purposes. No circulating tumor DNA assay is used to designate DNA repair status. All patients undergoing circulating tumor DNA testing will be designated as DRPro. These choices reflect the real world challenges of tumoral diagnostics in prostate cancer patients, yet utilizes our knowledge that most patients are DRPro. Of note, if circulating tumor DNA or metastatic site sequencing finds a BRCA1, BRCA2 or ATM mutation, the local study team is recommended to refer the patient to genetic counseling for further workup. For full discussion of DNA repair status designation, see Section 3.3.

1.2.1 **Rationale for patient population and single arm design**

The patient population studied is mCRPC patients who have effectively failed one or more prior lines of established mCRPC therapy. The studied agents are not anticipated to have overlapping resistance patterns with other mCRPC therapies, such that no specific mCRPC directed drug exposure is required or avoided. Patients treated with prior PARP inhibitors or DNA-damage response agents (e.g. cisplatin, carboplatinum) are excluded. The choice of at

least one prior therapy is to maintain clinical equipoise for a drug combination without previous record of effect, while acknowledging the known overlapping resistance patterns between current mCRPC directed therapies and also financial limitations some patients experience regarding access to second generation anti-androgens. Chemotherapy and its expected toxicities are also not preferred for many patients, allowing the study to be offered prior to chemotherapy. Two unique scenarios are patients who are treated with second-generation anti-androgen therapies (e.g. abiraterone) during the hormone-sensitive phase of disease or non-metastatic castration resistant phase of disease. Patients progressing while continually on these therapies have effectively failed one line of classical mCRPC therapy, and thus are allowed to enter directly into the study at diagnosis of mCRPC.

Clinically within prostate cancer, single agent DNA repair targeting in DRPro was unsuccessful with PARP inhibitor monotherapy, but showed some efficacy in DRDef [3]. Unfortunately, only ~20% of mCRPC patients are DRDef- leaving the majority of patients without benefit. There is preclinical support for activity with the combination in DRPro. With this clinical and preclinical support requiring multiple perturbations of DNA repair (either genetic or pharmacologic) for success, single agent AZD6738 is unlikely to be effective- hence why the combination only is being tested.

1.2.2 Rationale for olaparib dose

The starting olaparib dose is 300 mg by mouth, twice a day, for days 1-28 of a 28-day cycle. This dose is the active and tolerated dose seen previously in other DRDef or platinum sensitive cancers [10, 12]. It is tolerated with the below AZD6738 dose and schedule with hematologic toxicity being the main challenge.

1.2.3 Rationale for AZD6738 dose

The dose of AZD6738 is 160 mg by mouth daily for days 1-7 of a 28-day cycle. This dose maintains a mean steady state concentration above the IC_{90} for ATR *in vivo* during the treatment week. A one out of four weeks schedule is required to manage toxicity. Dose limiting toxicities are reviewed in Section 1.1.2.

1.2.4 Rationale for circulating correlative studies

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) are unique biologic samples as they attempt to recapitulate the tumor heterogeneity into a single blood draw. These liquid biopsy approaches provide an opportunity to develop blood-based predictive or prognostic biomarkers that could obviate the need for tumor-directed biopsies. By combining ctDNA with both morphologic and possible DNA/RNA-based analyses of CTCs, the mutational and transcriptional tumor landscape may be determined. Furthermore, evaluating the concordance of a serum sample to the metastatic biopsy will allow for both: validation of the liquid-based approach and likely identification of patients harboring DNA repair defects that are not present in the single metastatic site biopsied. These analyses will be collected prior to treatment in order to develop these assays as predictive biomarkers of response and during treatment to monitor alterations in circulating disease. CTC and ctDNA analyses will also be done at the end of treatment to explore mechanisms of resistance. These correlative studies are exploratory in nature only.

The ctDNA and CTC analyses to correlate with response to treatment and clinical characteristics of disease, will be done for all patients enrolled into treatment. DNA modifications of these samples (e.g., epigenetic or otherwise) and noncoding elements (e.g., telomere length, introns) may be investigated with the above goals in the future as excess tissue and blood specimens will be banked. Correlation of these tumor characteristics can also be compared retrospectively to each patient's clinical course. Published algorithms of the above data for olaparib response will be validated and new ones created/tested.

Previous tissue obtained either in routine care OR left over when the on-study biopsy was performed may be requested. This will be labeled by study ID only and may be utilized by the coordinating center or shared with sponsor. If samples are shared with sponsor, they will NOT be utilized for next generation sequencing analyses to avoid genetic privacy concerns. Patients may opt-out of the request for prior tissue and/or sharing of prior/study tissue with sponsor. Left over tissue from the biopsy will be sent to coordinating center (after sequencing completed at TEMPUS).

1.3 Benefit, Risk and Ethical Assessment

The combination of olaparib and AZD6738 has been demonstrated as safe and tolerable in patients with a range of solid tumors. Toxicity is manageable with effective monitoring of patients, especially effects on the bone marrow, and both IMPs may be dose modified if necessary. There is preclinical support *in vitro* for activity with the combination in DRPro and DRDef, with a paucity of existing clinical data for prostate cancer uniquely. PARP inhibition has demonstrated efficacy in DRDef prostate cancer patients but resistance still develops [3]. The AZD6738/olaparib combination has been explored clinically in the ongoing AstraZeneca phase I/IIa study, and found to be safe [13].

mCRPC is a challenging field as current therapies appear to have overlapping mechanisms of resistance (e.g. androgen receptor amplification for enzalutamide and abiraterone) and chemotherapy (e.g. docetaxel, cabazitaxel) is not viable nor preferred by many patients. Hence, it has created an opportunity to try novel combinations after failure of a single line of therapy. Resistance patterns may also be emerging earlier in the disease course as some mCRPC patients will have seen secondary hormonal agents earlier (mHSPC) and thus may benefit from trial agents in the frontline mCRPC setting.

2. STUDY OBJECTIVES

2.1 Primary Objective

Primary Objective:	**Outcome Measure:**
To determine the response rate of the combination of olaparib and AZD6738 in mCRPC patients who are DNA repair proficient (DRPro, e.g. intact ATM, BRCA1 or BRCA2).	The rate of response (CR/PR) per radiographic response according to RECIST v1.1 or PSA (≥50% decline) in DRPro patients.

2.2 Secondary Objectives

Secondary Objective:	Outcome Measure:
To determine the response rate of the combination of olaparib and AZD6738 in mCRPC patients who are DNA repair deficient (mono- or biallelic somatic ATM loss OR biallelic somatic loss of BRCA1 or BRCA2 OR known mono or biallelic germline loss of ATM, BRCA1, or BRCA2).	The rate of response (CR/PR) per radiographic response according to RECIST v1.1 or PSA (≥50% decline) in DRDef patients.
All of the below secondary objectives will be calculated for the DRPro, DRDef patients separately.	
Objective progression-free survival (combined radiographic and clinical progression-free survival)	The objective progression-free survival is the duration of time from start of treatment to date of progression (based only on radiographic progression or clinical decline/death).
Objective radiographic disease response rate	The rate of achieving a radiographic response according to RECIST v1.1.
PSA progression-free survival	Composite of survival and duration of PSA control as defined by time from start of therapy to first PSA increase ≥ 25% and ≥2 ng/ml above the nadir and confirmed by a second value at or beyond 4 weeks later.
PSA response rate for ≤ 0.2 ng/ml, 50% decline, 90% decline from entry PSA and confirmed 4 weeks later	The rate of achieving the aforementioned PSA value or percent decline compared to PSA at entry.
Duration of combined radiographic and PSA response	Time from first documented response (RECIST v1.1 CR/PR or PSA decline ≥50%) until death, recurrent or progressive disease (based on RECIST v1.1) or first PSA increase ≥ 25% and ≥2 ng/ml above the PSA nadir.

2.3 Safety Objectives

Safety Objective:	Outcome Measure:
To evaluate the quantitative and qualitative tolerability of the combination within the combined, DRPro and DRDef patients.	AE summaries and treatment exposure by genetic subtype

2.4 Exploratory Objectives

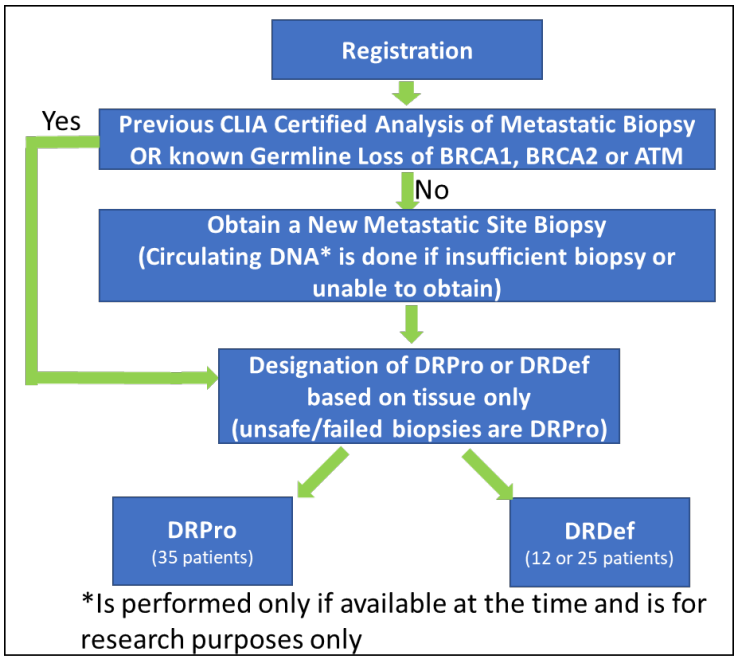
Exploratory Objective:	Outcome Measure:
To evaluate the predictive capacity of circulating analytes within both genetic cohorts.	Circulating tumor DNA sequencing/quantification, circulating tumor cell number, circulating tumor cell composite gene expression by pooled RT-PCR.

3. STUDY PLAN AND PROCEDURES

3.1 Overall Study Design and Flow Chart

This is a single-arm study evaluating the response of DRPro and DRDef patients with mCRPC. Patients whose DNA repair status is known or unknown may enroll. If they require biopsy, their DNA repair status is described and patient directed into the correct cohort. Patients are allowed to have one or more prior lines of therapy for mCRPC. If they became castration-resistant while on second generation androgen pathway inhibitors within the mHSPC phase of disease, they may enroll.

3.2 Registration Flow Chart



3.3 Patient Registration

Before initiating screening, the scope and requirement of the trial must be reviewed with each patient. Patients should understand the inherent risks of the trial therapies, required diagnostics (biopsy if needed), alternative treatment options, their right to privacy and also the right to withdraw from study for any reason. Once this is done and the patient is estimated to meet eligibility criteria (excluding the DNA repair status and completing washout period for prior drug or radiation- this may complete while awaiting biopsy/results), they may sign and date an IRB-approved inform consent which meets the requirement of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50). No study-specific procedures will be undertaken until a signed consent form has been completed.

Patient registration for this trial will be centrally managed by the Coordinating Center of the University of Michigan Rogel Cancer Center as described below.

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on a Screening and Enrollment Log.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been determined by the local site, a copy of the completed Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

The Multi-Site Project Manager (MSPM) of the Coordinating Center will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

An email will be sent by the MSC to the requesting site registrar to confirm patient registration and to provide the study identification number that has been assigned to the patient. In addition, a copy of the completed Eligibility Worksheet signed and dated by the MSPM, will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in a Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

3.3.1 Informed consent

Informed consent is obtained by following the procedures in Section 9.3 and within 24 hours after patients signs informed consent, sites will provide a complete signed informed consent form to coordinating site.

3.3.2 Confirmation of clinical/laboratory eligibility

After laboratory screening for eligibility is completed, an eligibility checklist (minus DNA repair status and time related events (washout, radiation, surgery)) will be submitted to the coordinating site. The coordinating site will review and, if eligible, the patient is enrolled in the trial.

If a prior biopsied mCRPC or mHSPC site was sequenced in a CLIA certified lab with a next-generation sequencing platform, that is adequate for DNA repair status determination and the report should be submitted to coordinating site for review. If the patient had a known germline loss of BRCA1, BRCA2, or ATM that is adequate (the official testing report must be submitted). If DNA repair status is unknown, patients should undergo genomic evaluation via a biopsy of a soft tissue metastatic deposit (preferred) or bone metastasis and submit it to Tempus Labs as specified in the laboratory manual. If the biopsy yields insufficient tissue or the biopsy itself is unable to be performed secondary to procedural safety as deemed by local PI, the patient may undergo (if available at the time) circulating tumor DNA/germline DNA testing per the lab manual. Due to the lack of predictive validation for circulating tumor DNA and delays in germline testing, any patient undergoing it will be designated DRPro (although

subgroup analyses can further explore its relevance). If the analysis or tumor based testing shows any potentially inheritable defect, the treating provider is recommended to consider sending the patient to a genetic counselor for review.

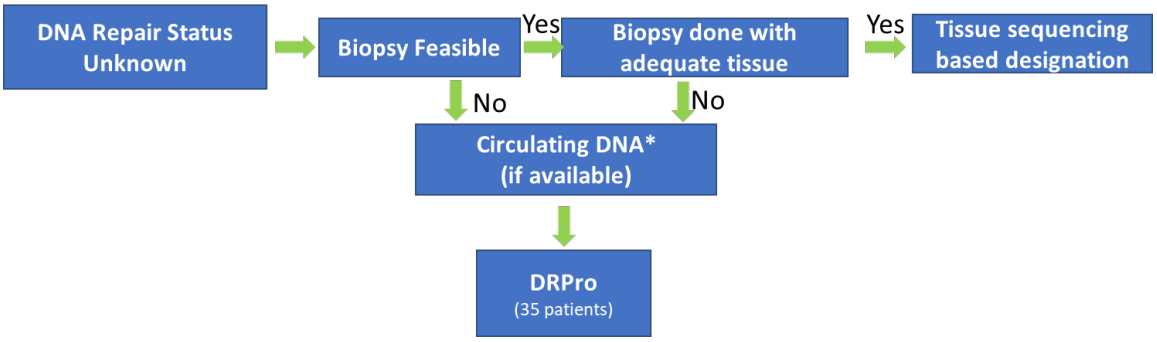
3.3.3 Confirmation of 12-lead ECG eligibility and safety

ECGs are required at **screening (triplicate)**, AND within **7 days prior to starting** study treatment (ok for same day as C1D1) AND when clinically indicated. The timing and number of ECGs may be adjusted in response to the emerging PK and safety profile. Twelve-lead ECGs will be obtained. All ECGs should be recorded with the patient in the same physical position. For screening, triplicate ECGs are required. After the screening of ECGs, only if the first ECG QTC is prolonged (>450 ms by Fridericia), then on two more ECG recordings separted by 5 minutes will be taken. If the on-study first ECG has a normal QTC, no further ECGs are required for that timepoint. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study, where feasible. After ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, PR, R-R, QRS and QT intervals and an overall evaluation will be recorded.

3.3.4 Registration biopsy

Biopsy tissue should be processed and shipped to Tempus Labs as specified in the laboratory manual. The coordinator for Tempus Labs will inform the coordinating site Project Manager as well as the participating site whether the patient has adequate tissue for analysis.

3.3.5 DNA repair designation flow chart



*Is for research purposes only, it is not required to be completed to be DRPro designated.

3.3.6 Molecular DNA repair status designation

DRDef requires mono or biallelic inactivation of ATM or biallelic inactivation of BRCA1 or BRCA2 via copy loss and/or loss of function mutations/insertions/deletions as interrogated by comparing the found alterations to published databases and primary literature by Tempus Labs. Germline loss of BRCA1, BRCA2 or ATM is adequate as it is known to uniformly be lost in the alternate allele for these patients. Monoallelic loss requires a deletion or mutation in the gene. A biallelic deleterious defect is characterized by 2 deletions, 1 deletion + 1 mutation, or

2 mutations. Variants of unknown significance do not qualify. See Section 3.3.5 for diagnostic workup to define DNA repair status.

3.3.7 **Anticipated enrollment**

The trial will stop accrual once the predesignated DRPro and DRDef patients have enrolled. If one arm closes due to complete accrual or futility, the alternate arm may continue to enroll. Patients must start therapy AFTER DNA repair designation is reported if one arm of the trial is closed or near closing (within 3 patients). Accrual for primary endpoint is 24 months duration of the study is 36 months.

4. PATIENT SELECTION CRITERIA

Subjects will be identified through routine care of patients within the participating tertiary cancer care centers. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances are there exceptions to this rule.

4.1 Inclusion Criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures
2. Male ages 18 years and older at time of signing the informed consent form
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 within 42 days prior to registration
4. Histologic or cytologic proof of prostate adenocarcinoma (excluding small-cell or neuroendocrine pathologies)
5. Metastatic prostate cancer on CT, MRI or Bone scan
6. Must have disease progression (while testosterone level is under 50 ng/dl) on prior therapy prior to study entry defined as one (or more) of the following:
    a. PSA progression defined as continuously rising PSA values measured a minimum of 1 week apart with a minimal starting value of 1.0 ng/mL
    b. Progression of bidimensionally measurable soft tissue or nodal metastasis by CT or MRI based on RECIST, v1.1
7. Prior treatment with at least one of the following:
    a. One line of therapy in mCRPC
    b. Second generation anti-androgen (e.g. abiraterone, enzalutamide or apalutamide) within the hormone-sensitive phase of disease AND progression occurs while on therapy
8. Patients must be withdrawn from prior therapy for ≥3 weeks (patients may remain on prior prednisone up to 10 mg total daily exposure at provider's discretion) at planned time of treatment start.
9. Agree to undergo a biopsy of at least one metastatic site (if feasible) to determine DNA repair status, unless prior metastatic tissue underwent next-generation sequencing in a CLIA certified lab or known germline loss of BRCA1, BRCA2 or ATM. If no site is reachable, or first biopsy insufficient/unsuccessful, circulating tumor DNA may be obtained.

10. Treated with continuous androgen deprivation therapy (either surgical castration or LHRH agonist/antagonist) with documented castrate level of serum testosterone (<50 ng/dL). A stable dose of bisphosphonate or denosumab for bone metastases should be continued as long as started at least 5 days prior to C1D1 planned start day.
11. At the time of planned treatment start (C1D1), at least 21 or more days will have elapsed from palliative radiation (with the exception of radiation to >30% of bone marrow or with a wide field of radiation, this requires 28 or more days).
12. Patient must have normal organ and bone marrow function measured within 42 days prior to registration as defined below
    a. Hemoglobin ≥10 g/dL (with no blood transfusion or erythropoietin use within the past 42 days)
    b. Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    c. Platelet count $\geq 100 \times 10^9$/L (with no platelet transfusions within last 42 days)
    d. Total bilirubin <1.5x ULN (unless the patient has documented Gilbert's disease and <2.0x ULN should be used)
    e. AST or ALT ≤ 2.5x ULN, unless liver metastases are present in which case they cannot be ≥5x ULN
    f. Glomerular filtration rate (GFR) ≥51 mL/min, as assessed using the Cockcroft-Gault equation
13. Estimated life expectancy ≥16 weeks
14. Male patients who are sexually active must be willing to use barrier contraception for the duration of the study and for 1 week after the last study drug administration, with all sexual partners. Male patients must use a condom during treatment and for 6 months after the last dose of study drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing potential and must not donate sperm for 6 months after the last dose of study drug. Female partners of male patients should also use a highly effective form of contraception (see Appendix C) for 6 months after the last dose of study drug(s) if they are of childbearing potential. True abstinence is an acceptable form of contraception and must be documented as such.
15. Patient is willing and able to comply with the protocol for the duration of the study, including undergoing biopsy (if warranted), treatment, scheduled visits and examinations

4.2 Exclusion Criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled.

1. A diagnosis of ataxia telangiectasia
2. Prior treatment with a PARP inhibitor (e.g. olaparib, veliparib, niraparib, rucaparib), AZD6738 or other DNA-damage response agents (e.g. cisplatin or carboplatin)
3. Cytotoxic chemotherapy, first- or second-generation antiandrogen or CYP17 inhibitors are not permitted within 21 days or 5 half-lives of registration (whichever is longest) of planned treatment start. For clarity, enzalutamide requires 5 weeks washout.
4. Major surgery < 2 weeks prior to enrollment; patients must have recovered from any effects of major surgery
5. Persistent toxicities (≥CTCAE Grade 2) caused by previous cancer therapy, besides Grade 2 alopecia and Grade 2 neuropathy (these are allowed).

6. Patients with current or prior MDS/AML or with features suggestive of MDS/AML
7. Any other malignancy which has been active or treated within the past 3 years, with the exception of non-melanomatous skin cancer, or Ta bladder cancer
8. Patients with active brain metastases are excluded because of unknown penetration into the CNS. A confirmatory scan for asymptomatic patients is not required. Patients with a history of treated central nervous system (CNS) metastases are eligible provided they meet all of the following criteria: disease outside the CNS is present, no clinical evidence of progression since completion of CNS-directed therapy, minimum 3 weeks between completion of radiotherapy and registration and recovery from significant (Grade ≥ 3) acute toxicity with no ongoing requirement for >10 mg of prednisone per day or an equivalent dose of other corticosteroid. If a patient must remain on steroids, they must have started the steady dose at least 28 days prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days prior to study treatment.
9. Any of the following cardiac disease currently or within the last 6 months:
    a. Unstable angina pectoris
    b. Congestive heart failure (by New York Heart Association ≥ Class 2) or known reduced LVEF < 55%
    c. Acute myocardial infarction
    d. Conduction abnormality not controlled with pacemaker or medication (e.g. complete left bundle branch block or third-degree heart block)
    e. Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible).
    f. Uncontrolled hypertension (Grade 2 or above) requiring urgent (for example, adjusting medications within 24 hours) clinical intervention
    g. Patients at risk of brain perfusion problems, e.g. TIAs or history of pre-syncope or syncopal episodes unexplained by reversible causes
10. Mean resting corrected QT interval >450, obtained from 3 ECGs 2-5 minutes apart using the Fredericia formula. Absence of any factors that increase the risk of QTc prolongation or risk of arrhythmic such as congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 year of age. Patients with relative hypotension (<90/60 mmHg) or previously known clinically relevant orthostatic hypotension defined as a postural hypotension ≥20 mmHg
11. Concomitant use of known potent or moderate cytochrome P (CYP) 3A inhibitors (e.g. itraconazole, ciprofloxacin, diltiazem) require 2-week washout prior to planned C1D1. Concomitant use of strong or moderate CYP3A inducers (e.g. phenobarbital, enzalutamide, modafinil require 5-week washout for enzalutamide or phenobarbital and 3 week washout for all others. See Appendix B for further information.
12. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases that places the patient at unacceptable risk of toxicity or non-compliance. Examples include, but are not limited to, active bleeding diatheses, renal transplant, uncontrolled major seizure disorder, severe COPD, superior vena cava syndrome, extensive bilateral lung disease on High Resolution CT scan, severe Parkinson's disease, active inflammatory bowel disease, psychiatric condition, immunocompromised patients or active infection including any patient known to have hepatitis B, hepatitis C and human

immunodeficiency virus (HIV) or requiring systemic antibiotics, antifungals or antiviral drugs. Screening for chronic conditions is not required.

13. A known hypersensitivity to olaparib, AZD6738 or any excipient of the product or any contraindication to the combination anti-cancer agent as per local prescribing information
14. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with the absorption of the study medication, refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of AZD6738
15. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
16. Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no.12)
17. Involvement in the planning and/or conduct of the study
18. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.
19. Previous enrolment in the present study.
20. Has received a live vaccination with 2 weeks of enrollment.

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.7.

4.3 Restrictions During the Study

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

- Patients must fast (water to drink only) from at least 2 hours prior to taking all doses of AZD6738 and also for 1-hour post-dose.

- Olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

- It is recommended that AZD6738 is taken at the same time as the morning dose of olaparib and with fasting at least 2 hours prior to taking the dose and at least 1 hour afterwards. The second dose of olaparib may be taken with or without food

- If vomiting occurs shortly after AZD6738 or olaparib is swallowed, the dose should only be replaced if all of the intact tablets can be counted and then treatment resumed with the following scheduled dose. The scheduled dose can be taken up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and patient should continue with next dose at allotted time.
- Patients should not consume grapefruit juice or Seville oranges (including marmalade, juice, etc.) while participating in the study.

- Patients should be careful with driving within the first few days of starting therapy (cycle 1 only) due to risk of low blood pressure since tolerance is unknown.
- Precautions are advised to limit duration of sun exposure to skin with protective clothing and sunscreen.

4.3.1 Contraception

Male patients must use a condom during treatment and for 6 months after the last dose of study drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (as described in Appendix C) if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking study drug(s) and for 6 months following the last dose of study drug(s). True abstinence is an acceptable form of contraception. Please refer to Appendix C for further details

4.3.2 Concomitant treatments

AZD6738 is an investigational drug for which no data on *in vivo* interactions are currently available. Potential interaction is considered on the basis of preclinical *in vitro* data only.

The lists of CYP and transporter inhibitors/inducers, and CYP and transporter substrates are available in **Appendix B**. They are not exhaustive and the absence of a drug from these lists does not imply that its combination with AZD6738 is safe. If AZD6738 is being administered in combination, potential interactions of the combination partner should also be considered. **Olaparib** also has concomitant interactions and may require dose reduction if a strong or moderate CYP3A is required for a short period while on study.

- The principal enzyme for metabolizing AZD6738 is CYP3A, olaparib is also metabolized similarly Subjects should avoid concomitant drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A activity from the time they enter the screening period until 28 days after the last dose of study treatment.
- Prior to study medication, use of potent inducers or inhibitors of CYP3A are not permitted. For subjects taking any of these drugs (examples provided in **Appendix B**) the required wash-out periods before starting AZD6738 is described.
- While on study medication, if there is no suitable alternative concomitant medication other than a potent inhibitor of CYP3A, the investigator **must** interrupt AZD6738 for the duration of the potent CYP3A inhibitor and wait for the required wash-out period (five half-lives) before dosing AZD6738 again. If potent CYP3A inducers are considered necessary for the patient's safety and welfare, this may diminish the clinical efficacy of AZD6738 and the patient should be monitored carefully for any change in the efficacy of study treatment. Olaparib may also require adjustment. Refer to **Appendix B** for additional guidance.
- AZD6738 is a Pgp substrate. Co-administration of Pgp inhibitors or inducers may affect exposure to AZD6738 and, therefore, should be minimized if possible. Refer to **Appendix B** for additional guidance.

- AZD6738 is a substrate and inhibitor of breast cancer resistance protein (BCRP). Co-administration of BCRP inhibitors or inducers may affect exposure to AZD6738; therefore, it is recommended that the investigators should interrupt AZD6738 for the duration of on treatment necessary BCRP inhibitor or inducer and wait for the required wash-out period of the BRCP modulator (five half-lives) before dosing AZD6738 again. AZD6738 also may increase the serum levels of BCRP substrates. Refer to **Appendix B** for additional guidance.
- AZD6738 is a potential inducer of CYP3A4 and CYP2B6. Caution should be applied with co-administration of drugs that are either completely metabolized by CYP3A4 and/or CYP2B6, or that are substrates of CYP3A4 and/or CYP2B6 and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolized by CYP3A4 and/or CYP2B6 may be reduced. Refer to **Appendix B** for additional guidance.
- AZD6738 is an inhibitor of OATP1B1. Caution should be applied with co-administration of substrates of OATP1B1 as AZD6738 may increase their exposure. Refer to **Appendix B** for additional guidance.
- The use of herbal supplements or 'folk remedies' (and medications and foods that significantly modulate CYP3A activity) is not allowed.
- Anticoagulation therapy: subjects on warfarin may participate in this trial but it is recommended that their INR is monitored more frequently.
- Primary G-CSF and erythropoietin use is not allowed. Secondary G-CSF may be used if required.
- Radiotherapy is not permitted during the study with the exception of palliative radiotherapy for symptom control (drug dosing will need interrupting during this period)
- No other chemotherapy (bone supportive agents are allowed), hormonal therapy (besides LHRH agonist/antagonist), other investigational product or live virus or bacterial vaccines are permitted (killed vaccines are allowed) other than the combination agent(s) in the study

5. STUDY CALENDAR

	Screening (Day -42 to Day -1)	Cycle 1[m], 2[m]		Cycle 3+ Day 1[m] (-5 to +3d)	End of Treatment, 30 (±3) Day FU[m]	Long-term FU[j]
		Day 1[m] (±3day for c2)	Day 8[m] (±3 day)			
Informed Consent	X					
Medical/Surgical History, Demographics, Height Prior Histology (either report or clinician note as source)	X					
Biopsy of Metastatic Disease	X[a]					
Peripheral blood for germline and/or circulating tumor DNA	X[b]					
PE, Vitals[i], Weight	X	X[m]	X[m]	X[m]	X[m]	
Performance Status	X	X	X	X	X	
Adverse Event, Toxicity Evaluations		X	X	X	X	
Medication Review	X	X	X	X	X	
Study Drug[c]		X	X	X		
Radiologic evaluations and measurements[d]	X (Must be ≤4 weeks from C1D1 or repeated)[k]			X[e]		
ECG	X (triplicate)	X[g] (C1D1 only)				
Serum Chemistry[f], LDH	X	X	X (optional C2D8)	X	X	
PT (INR), APTT, Urinalysis[h]	X					
CBC with Differential	X	X	X (optional C2D8)	X	X	
PSA	X	X		X	X	

	Screening (Day -42 to Day -1)	Cycle 1[m], 2[m]		Cycle 3+ Day 1[m] (-5 to +3d)	End of Treatment, 30 (±3) Day FU[m]	Long-term FU[j]
		Day 1[m] (±3day for c2)	Day 8[m] (±3 day)			
Testosterone	X					
Circulating Correlatives		X[n]		C3D1 only[n]	X[n]	
Long-term follow-up for MDS/AML or new primary malignancy reporting						X

a. Biopsy must be done after patient has consented and registered to the study (unless pre-existing, CLIA certified lab, next-generation sequencing of metastatic mCRPC biopsy has been completed or mCRPC tissue available to submit for testing). Submitted tissue must be deemed adequate or fully reported prior to starting therapy.

b. Peripheral blood is sent for either germline comparison (if tissue also completed) or exploratory analysis of circulating tumor DNA and germline DNA if biopsy failed or is unsafe (and analysis available). If the biopsy is attempted and has insufficient tissue, new blood may not need to be redrawn as it was sent with biopsy.

c. For drug schedule see Section 1.2.

d. Radiographic evaluation will include radionuclide bone scan, CT or MRI of abdomen and pelvis, and CT, CXR or MRI of the chest as appropriate. All disease sites must be assessed using the same methodology as performed at baseline. At the discretion of the investigator, additional radiological evaluations may be performed at an unscheduled time point.

e. While receiving therapy, radiologic tests are performed every 8 weeks (±1 week) from C1D1. After the third scanning timepoint (~6 months), radiologic tests are performed every 12 weeks (±1 week) from C1D1.

f. Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, potassium, total protein, SGOT (AST), SGPT (ALT), sodium,

g. ECG is required ≤7 days of C1D1(C1D1 is adequate). Within the study, triplicate is not required unless the first ECG has a prolonged QTC per section 3.3.3.

h. Coagulation: activated partial thromboplastin time (APTT) will be performed at screening and if clinically indicated; international normalized ratio (INR) will be performed at screening and if clinically indicated. Patients taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Each coagulation test result will be recorded in CRF. Urinalysis will assess Hb/erythrocytes/blood, Protein/Albumin, and Glucose and should be performed at screening. After screening, urinalysis will only be required if clinically indicated.

i. Vitals include body temperature, blood pressure, pulse, respiratory rate, weight, height

j. Follow all patients for MDS/AML and new primary malignancy assessment for up to 5 years after the patient completes the study per Section 7.7.1.
k. To accommodate biopsy timing, the **screening** CT and bone scans to enroll allow for scans up to 6 weeks. If by the time therapy starts (to accommodate delays) prior scans will be >4 weeks from the planned start date of treatment, they must be repeated prior to C1D1 (≤4 weeks).
m. Due to COVID 19 exposure risks AND for ease of patient participation, virtual visits are allowed for ALL visits except C1D1 (with windows of ±3 days within C1 and C2, and -5: +3 for C3+). Regarding labs, local labs may be used with the same windows as visits (except for C2D8 where labs are optional). A single lab is preferred if possible, to minimize interlab variability. When the Morgan lab (see footnote[n]) is open, C1, C3D1 and EOT labs are preferred to be done at primary research sites to allow shipping of correlatives (but it is up to treating provider to balance tertiary care center COVID risks at that moment in time). Virtual visits should entail a video link with patients (via established, HIPAA compliant video visits). Phone visits are not preferred. For virtual visits, PE, weight and vitals will not be collected and are NOT deviations. See section 5.3.3 for drug shipping guidance.
n. Due to COVID 19 exposure risks and guidance from the University of Michigan, the Morgan lab may have intermittent availability. The coordinating center (UMCCC) will update all sites with the status of the Morgan lab by email to keep sites aware on whether to collect specimens or not. This flexibility will avoid repeat amendments and IRB backlogs.

5.1 Subject Enrollment and Initiation of Study Therapy

Subjects will be identified through routine care of patients within the participating cancer centers. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study.

5.2 Procedures for Handling Subjects Incorrectly Enrolled or Initiated on Investigational Product

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. Where a subject does not meet all the eligibility criteria and incorrectly started on treatment, the Investigator should inform the coordinating site and PI immediately, and a discussion should occur between regarding whether to continue or discontinue the patient from treatment. The coordinating site must ensure all decisions are appropriately documented.

5.3 Treatments

5.3.1 Identity of investigational products

The AstraZeneca Pharmaceutical Development R&D Supply Chain or a third party distributor/contractor will supply AZD6738 and olaparib.

Investigational products	Dosage form and strength(s)
AZD6738	*20, or 80 tablet*
Olaparib	*100 or 150 mg tablet*

5.3.2 Treatment plan

Agent	Dose	Route	Schedule	Cycle Length
AZD6738	160 mg	Oral	Once daily, Days 1-7	28 Days
Olaparib	300 mg	Oral	Twice daily, Days 1-28	

5.3.3 Agent administration + distribution

All treatment is rendered on an outpatient basis. Reported side effects and potential risks are described in Section 6.1/6.2 and dose modifications in Section 5.4. No other investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy (excluding LHRH agonists/antagonists). The research staff will provide detailed instruction and training for the handling of study drugs and administration at the beginning of the study to each patient. All dosages prescribed and dispensed to the patient and all dose changes during the study are recorded. The patient should contact the Investigator if he is unable to take the study drugs as prescribed.

Study drug may be shipped by each site's research pharmacy (if they are able to) via certified temperature-controlled container for overnight delivery, with tracking number and delivery signature required. Consultation with local research pharmacy is required and coordinating center must be notified that the local IRB and site is able to do this PRIOR to implementing site-> subject shipments. Sites are required to submit to coordinating center the subject diary and associated shipment processes for each cycle. The drug dispensation log must be updated as required noting direct shipment and copy of signature of receipt is encouraged to be obtained (if possible), placed in study records and be available for monitoring. Any non-receipt by subject/household must be reported to study staff locally so that shipment can be tracked and drug accounted for. Any missed dose of study medication is to be managed per protocol.

5.3.4 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

Each bottle of AZD6738 and olaparib will have an investigational product label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. The label will include the dosing instructions and a space for the enrollment code (E-code) to be completed at the time of dispensing.

The label will include the following information:

blank lines for quantity of tablets to be taken
enrollment code (E-code)
date of dispensing
Instructions stating that the AZD6738 tablets should be taken at approximately the same time each morning or evening

5.3.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the Investigator Brochure specifies the appropriate storage.

5.4 Management of Toxicity

5.4.1 Toxicities that require discontinuation from protocol therapy

Any toxicity observed during the course of the study should be managed in the first instance by interruption of the dose of study treatment and dose reductions if necessary. Repeat dose interruptions are allowed as required for a maximum of 28 days on each occasion. Treatment must be interrupted until the patient recovers completely or the toxicity reverts to NCI CTCAE grade 1 or 2 (depending on toxicity) or to the baseline CTCAE grade. If the required interruption is any longer than 28 days due to toxicity, the patient must be removed from the study. If at any point during study treatment, it becomes apparent that the tumor is not coming under control, patients are to be removed from study and treated as clinically indicated.

Protocol therapy should be discontinued if a patient experiences:

- Any CTCAE Grade 4 toxicity with the exception of:
  - CTCAE Grade 4 neutropenia of 5 days or fewer duration
  - CTCAE Grade 4 nausea, vomiting or diarrhea that resolves to Grade 3 in less than 72 hours in patients who have not received optimal anti-emetic or anti-diarrheal therapy
  - CTCAE Grade 4 laboratory abnormalities that can be readily corrected within 72 hours and do not result in hospitalization
- CTCAE Grade 3 or 4 thrombocytopenia with bleeding requiring hospitalization

5.4.2 Dose levels for olaparib and AZD6738

Both drugs have two levels allowed for dose reductions and may be dose reduced stepwise per instructions below. Once a dose is reduced, escalation is not permitted. All dose modification and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the eCRF. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion.

AZD6738 has a unique aspect in that its hematologic toxicity (specifically neutropenia, leukopenia, thrombocytopenia, see section 5.4.5) is schedule rather than dose-dependent. For hematologic toxicities related to AZD6738 requiring a single dose reduction, the schedule is adjusted rather than the daily dose (see Table 1). Non-hematologic toxicities requiring dose reductions (as both drugs would be lowered by one level), daily dose is lowered rather than schedule. If both a hematologic (related to AZD6738 per 5.4.5) AND non-hematologic Grade 3+ toxicity requiring dose reduction occur concurrently, both drugs are dose reduced. Olaparib is reduced by one dose level, while if AZD6738 is on dose level 0 is reduced to dose level -2 at first reduction.

TABLE 1 Dose Modification Table for AZD6738

Dose Level	AZD6738
0	160 mg daily Days 1-7
-1 (Hematologic toxicity)	160 mg daily Days 1-4
-1 (Non-hematologic toxicity)	120 mg daily Days 1-7
-2	120 mg daily Days 1-4

TABLE 2 Dose Modification Table for Olaparib

Dose Level	Olaparib
0	300 mg BID Days 1-28
-1	250 mg BID Days 1-28
-2	200 mg BID Days 1-28

5.4.3 Hematologic Day 1 dosing requirement

Hematologic toxicity is anticipated to be the biggest challenge. To minimize this risk, there are clear Day 1 criteria (for any cycle) for both ANC and platelets. Both an ANC over 1000/μL and platelets over 75,000/μL are required to start each cycle. If either parameter is not met, treatment is delayed. If the patient has not recovered after 28 days, they are removed from protocol and please see section 5.13 for further hematologic workup.

TABLE 3 Day 1 minimum hematologic criteria

Treatment day blood counts and toxicity			
ANC		**Platelets**	**Action**
≥ 1000/μL	AND	≥ 75,000/μL	No dose modification or interruption
< 1000/μL	OR	<75,000/μL	Delay by 1 week intervals until recovery

5.4.4 Management of anemia

Olaparib has shown the most suppression of red blood cells in prior studies, such that it is first reduced in lower risk anemia scenarios. At development of anemia, appropriate supportive treatment should be considered (per local guidelines) and alternate cause evaluation considered (e.g. iron, vitamin B12, folate, hypothyroidism). Investigator judgement to continue study treatment with or without supportive treatment (e.g. transfusion) or interrupt dose for a maximum of 4 weeks per guidance below. The use of erythropoietin is not allowed.
For cases where patients develop prolonged hematologic toxicity causing >2-week interruption/delay in study treatment for CTCAE Grade 3 or worse anemia and/or blood transfusion dependence, refer to Section 5.4.14 for workup to consider.

Note, if at any time a dose reduction for a drug is required and the patient is already at dose level -2 for that drug, the patient must be removed from study.

Symptoms related to the Anemia (e.g. fatigue, shortness of breath) are designated by treating provider.

ASYMPTOMATIC Grade 2 Anemia (Hgb<10 and Hgb≥8 g/dL):

Asymptomatic Grade 2 anemia may be monitored and treatment continued without required delay or dose reduction. Delay, dose reduction and transfusions may be done at provider's discretion.

SYMPTOMATIC Grade 2 Anemia (Hgb<10 and Hgb≥8 g/dL) or ANY Grade 3 Anemia (Hgb<8 g/dL):

First episode:

1. Symptomatic Grade 2:

   A treatment delay up to 28 days maximum (with or without blood transfusion) to allow resolution to asymptomatic Grade 2, Grade 1 or lower. Olaparib may be dose reduced or continued at current dose level.

2. Grade 3:

   Treatment is delayed to allow resolution to asymptomatic Grade 2, Grade 1 or lower (up to 28 days maximum). Transfusions may be done at provider's discretion. Upon recovery, olaparib is reduced by one dose level (if possible).

Second episode:

3. Symptomatic Grade 2:

   A treatment delay up to 28 days maximum (with or without transfusion) to allow resolution to asymptomatic Grade 2, Grade 1 or lower. Upon recovery, Olaparib is dose reduced by one level (if possible).

   1. If olaparib was at full dose, AZD6738 dose/schedule is unchanged.
   2. If olaparib was at dose level -1, AZD6738 is moved down one dose level. Either from dose level 0 to dose level -1 (hematologic toxicity, which is 160 mg daily Days 1-4) OR from dose level -1 (hematologic or non-hematologic) to dose level -2.

4. Grade 3:

   Treatment is delayed to allow resolution to asymptomatic Grade 2, Grade 1 or lower (up to 28 days maximum). Transfusions may be done at provider's discretion. Upon recovery, olaparib is reduced by one dose level (if possible).

   1. AZD6738 is moved down one dose level. Either from dose level 0 to dose level -1 (hematologic toxicity, which is 160 mg daily Days 1-4) OR from dose level -1 (hematologic or non-hematologic) to dose level -2.

Third episode:

5. Symptomatic Grade 2 or Grade 3:

   A treatment delay up to 28 days maximum (with or without transfusion) to allow resolution to asymptomatic Grade 2, Grade 1 or lower. Upon recovery, Olaparib is dose reduced by one level (if possible).

   1. AZD6738 is moved down one dose level to dose level -2 (if possible).

   If no further reductions are possible because olaparib or AZD6738 are already at dose level -2, the patient should be removed from the study.

Fourth episode:

6. Symptomatic Grade 2: Patient is removed from study
7. Grade 3: Patient is removed from study

Any episode of Symptomatic Grade 2 or Grade 3 anemia in conjunction with Grade 2 or higher neutropenia, leukopenia or thrombocytopenia

Treatment is delayed to allow resolution of anemia to asymptomatic Grade 2, Grade 1 or lower and thrombocytopenia/leukopenia/neutropenia to Grade 2 or lower (up to 28 days maximum). Provider may do transfusions at their discretion. Upon resumption of therapy, olaparib is dose reduced by one level. AZD6738 is dose reduced by one dose level. Either from dose level 0 to dose level -1 (hematologic toxicity, which is 160 mg daily Days 1-4) OR from dose level -1 (hematologic or non-hematologic) to dose level -2.

5.4.5 Management of neutropenia, leukopenia and thrombocytopenia

Adverse events of neutropenia and leukopenia should be managed as deemed appropriate by the Investigator with close follow up and interruption of study drug if CTCAE Grade 3 or higher occurs. For toxicity of Grades 1-2, especially if more than one toxicity is present, drug can be interrupted at Investigator discretion. Interruption can be up to a maximum of 4 weeks. Appropriate supportive treatment and causality should be considered. For CTCAE grade 3-4 toxicities, dose interruption until recovered to grade 1 or 2 or better (up to a maximum of 4 weeks) should be done. If repeat occurrences, then dose reduce olaparib to dose level -1 and AZD6738 to dose level -1 (hematologic) per above. If a second event happens, dose reduction of olaparib to dose level -2 and AZD6738 to dose level -2 should be done. If either dose does not have another dose level below, they should be removed from study.

G-CSF should be given according to local hospital guidelines for febrile neutropenia but not within 24 hours of the last dose of study treatment unless absolutely necessary. Primary prophylaxis with GCSF is not allowed. After G-CSF, treatment can resume at the earliest 24 hours after last G-CSF dose OR 7 days for pegylated G-CSF.

For cases where patients develop prolonged hematological toxicity (>2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse), refer to Section 5.4.14.

5.4.6 Management of non-hematologic toxicity

Acute toxicities should be managed as medically indicated, with temporary suspension of IP and initiation of supportive care as clinically indicated by the treating physician. Treatment and study participation must be stopped for Grade 4 non-hematologic toxicity excluding; a) Grade 4 nausea, vomiting, diarrhea that resolves to Grade 3 in less than 72 hours in patients who have not received optimal anti-emetic or anti-diarrheal therapy and b) Grade 4 laboratory abnormalities that can be readily corrected within 72 hours and do not result in hospitalization. At the first occurrence of CTCAE grade 3 or 4 non-hematologic toxicity that resolves to CTCAE grade 1 or 2 with supportive measures and treatment hold under 28 days, treatment may be resumed. At the resolution of the first occurrence of a toxicity, a change to dose is not automatically required unless indicated by the specific nature of the AE in severy or recurrence in view of provider. At the second occurrence, upon resolution of toxicity, it is suggested that olaparib AND AZD6738 should be dose reduced by one dose level (if possible). If no dose reduction is possible (e.g. either drug already at dose level -2), the patient is removed from study. If the required interruption is longer than 28 days due to toxicity, the patient must be removed from the study treatment unless approved by the Principal Investigator.

5.4.7 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in all study treatment dosing is recommended and further diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis. In cases of confirmed pneumonitis (as known toxicity with olaparib), treatment is to discontinue.
The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath, pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2; Saturation of peripheral oxygen (SpO2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
    - ILD markers (KL-6, SP-D) and β-D-glucan
    - PSA

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted at the same dosing, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

5.4.8 **Management of nausea and vomiting**

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered (e.g. dopamine receptor antagonist, antihistamines or dexamethasone).

Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e. 2 pieces of toast or biscuits). See section 5.4.6 for exclusion criteria to Grade 4 trial discontinuation.

5.4.9 **Management of diarrhea**

Vigorous anti-diarrheal treatment loperamide (Imodium) is required at the first onset of diarrhea according to American Society of Clinical Oncology (ASCO) guidelines unless systemic infection is suspected and requires rule out per treating physician. Oral loperamide (Imodium) should be used first and with repeat episodes per package guidelines. The first dose of loperamide may be lowered to 2 mg if the diarrhea is recurrent and if in the opinion of the treating physician, the diarrhea is not severe.

Patients should be instructed to notify the Investigator or research staff of the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhea within 24 hours of using loperamide or other prescribed anti-diarrheal medications.

If diarrhea is severe (i.e. requiring intravenous [IV] rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for IV hydration and correction of electrolyte imbalances per provider discretion. Doses should be held for Grade 3 or 4 toxicity. See section 5.4.6 for exclusion to Grade 4 trial discontinuation regarding diarrhea.

5.4.10 **Renal toxicity**

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 mL/min), retesting should be performed promptly.

A one step dose reduction is recommended for patients who develop moderate renal impairment (calculated CrCl by Cockcroft-Gault equation of between 31 and 50 mL/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg BID, see Table 2.

Olaparib has not been studied in patients with severe renal impairment (CrCl ≤30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

5.4.11 **Management of hepatic toxicity**

Drug should be stopped if

- ALT or AST or ALP* > 5 × ULN
- ALT or AST or ALP* > 3 × ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (>5%)
- [ALT or AST > 3 × ULN] and [total bilirubin > 2 × ULN or INR >1.5 (unless patient is receiving warfarin) or other evidence of impairment to the synthesis function of the liver]

  * In the presence of bone metastasis, assess bone specific isoform of raised ALP in the presence of a raised gamma-GT (to ensure the ALP change is specific to the liver).

Please refer to Appendix A "Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law".

5.4.12 **Management of cardiovascular abnormalities**

Cardiovascular toxicity is potentially associated with AZD6738. Either clinically significant hypotension (defined as an asymptomatic decrease of more than 20 mmHg in systolic blood pressure to below 70 mmHg persisting for at least 10 minutes) or symptomatic orthostatic fall in systolic blood pressure (of more than 20 mmHg compared to resting supine systolic blood pressure) should be managed with drug interruptions or reductions as per investigator's discretion.

5.4.13 **Drug interruptions for intercurrent non-toxicity related events**

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 28 days for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Study Physician. All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery and restarted 10 days post-surgery if the wound has healed. If the wound has not healed well, a further 7 days may be allowed and the patient can recommence study drug(s) if there is no evidence of disease progression. No stoppage of study treatment is required for any needle biopsy procedure. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

TABLE 4 Dose interruption and stopping criteria

Event	Action
Surgery	Interrupt both drugs (maximum 28 days) and resume at full dose. Both drugs should be stopped 3 days prior to surgery and resumed approximately 10 days later. If the wound has not healed a further 7 days are permitted prior to restarting combination. No stoppage is required for biopsy procedures.
Vomiting	If vomiting occurs shortly after study medication is swallowed, the dose should only be replaced if all of the intact tablets can be counted. Resume with the following scheduled dose.
Missed dose	Allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and patient should continue with next dose at allotted time.

5.4.14 Management of prolonged hematologic toxicities while on study treatment

If a patient develops prolonged hematological toxicities (due to either AZD6738 or olaparib or both drugs) such as:

- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse neutropenia (ANC < 1 x 10^9/L).
- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L).

Check weekly differential blood counts including reticulocytes and peripheral blood smear for prolonged hematologic toxicities requiring delays. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to CTCAE Grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed. The effect if any of AZD6738 on the bone marrow in terms of prolonged suppression is unknown.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section above. 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. Full reports must be provided by the investigator for documentation on the Patient Safety database. These data are not required to be entered into CRF.

5.5 Treatment Compliance

To safely participate in a clinical study, all patients should complete pill diaries and planned laboratory studies. Unused drug will be returned to the study team who will contact the sponsor for instruction or follow local standard operating practices.

5.6 Discontinuation of Investigational Product

Subjects may be discontinued from protocol treatment in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the study protocol
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Disease Progression (as defined by Section 7.6.7). In the absence of other indicators of disease progression, therapy should not be discontinued based on PSA rise alone.

5.6.1 Procedures for discontinuation of a subject from investigational product

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The Principal Investigator/Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They should also immediately inform Sponsor of the withdrawal. Adverse events will be followed up for 30 days post last dose and all unused study drug should be returned by the subject.

If a subject is withdrawn from study, see Section 5.7.

5.6.2 Duration of follow-up

Patients will be followed for 30 days after removal from treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

All patients should be followed for MDS/AML and new primary malignancy assessment for up to 5 years after the patient completes the study per Section 7.7.1.

5.7 Patient Removal from Study

5.7.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore will not be treated. Screen failures should be documented on the Screening and Enrollment Log. These patients will not have a study identification number assigned to them and will not receive study treatment.

5.7.2 **Off study criteria**

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral, administrative reasons or progression. The reason(s) for discontinuation from study will be documented and may include:

- Patient withdraws consent (termination of treatment and follow-up);
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
- Patient is unable to comply with protocol requirements;
- Treating physician views continuation on the study would not be in the patient's best interest;
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- Lost to Follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented;

Termination of the study by The University of MichiganPatient completes protocol treatment and follow-up criteria

5.8 **Patient Replacement**

Patients who are enrolled in the study but do not start treatment with Olaparib, will be replaced and not included in analyses.

6. DRUG INFORMATION

6.1 Olaparib

Other names for the drug: AZD2281

Description: Olaparib is a potent PARP inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

Mechanism of Action: Olaparib inhibits PARP enzymes (including PARP1, PARP2, and PARP3. PARP enzymes), which are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair.

Absorption: Following oral administration of olaparib tablets, absorption is rapid with peak plasma concentrations typically achieved between 1 to 3 hours after dosing. On multiple dosing there is no marked accumulation (accumulation ratio of 1.4 – 1.5 for twice daily dosing), with steady state exposures achieved within 3 to 4 days.

Limited data suggest that the systemic exposure (AUC) of olaparib increases less than proportionally with dose over the dose range of 100 to 400 mg, but the PK data were variable across trials.

Co-administration with a high fat meal slowed the rate (Tmax delayed by 2 hours) of absorption, but did not significantly alter the extent of olaparib absorption (mean AUC increased by approximately 20%)

Distribution: Olaparib had a mean (± standard deviation) apparent volume of distribution at steady state of 167 ± 196 L after a single 400 mg dose of olaparib. The *in vitro* protein binding of olaparib at plasma concentrations achieved following dosing at 400 mg twice daily is approximately 82%.

Metabolism: *In vitro*, CYP3A4 was shown to be the enzyme primarily responsible for the metabolism of olaparib.

Excretion: A mean (± standard deviation) terminal plasma half-life of 11.9 ± 4.8 hours and apparent plasma clearance of 8.6 ± 7.1L/h were observed after a single 400 mg dose of olaparib.
Following a single dose of ^{14}C-olaparib, 86% of the dosed radioactivity was recovered within a 7-day collection period, 44% via the urine and 42% via the feces. The majority of the material was excreted as metabolites.
Based on preliminary data from a dedicated renal impairment trial, the mean AUC and Cmax of olaparib increased by 1.5and 1.2-fold, respectively, when olaparib was dosed in patients with mild renal impairment (CLcr = 50-80 mL/min; N=14) compared to those with normal renal function (CLcr >80 mL/min; N=8). There are no data in patients with CLcr < 50 mL/min or in patients on dialysis.

Side effects: The most common adverse reactions include GI distress (constipation, decreased appetite, diarrhea, indigestion, nausea, vomiting), dysgeusia, hematologic effects (anemia, leukopenia, neutropenia), headache, pneumonitis/cough/URI, arthralgias/myalgia and fatigue. Rare cases of myeloid leukemia have been observed also.

Drug Interactions: *In vitro*, olaparib was an inhibitor of CYP3A4 and an inducer of CYP2B6 at higher concentrations than are clinically achieved. Olaparib produced little/no inhibition of other CYP isozymes. *In vitro* studies have shown that olaparib is a substrate of CYP3A4.

Based on the data from a drug-interaction trial (N=57), the AUC and Cmax of olaparib increased by 2.7- and 1.4-fold, respectively, when olaparib was administered in combination with itraconazole, a strong CYP3A inhibitor. Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that a moderate CYP3A inhibitor (fluconazole) may increase the AUC and Cmax of olaparib by 2- and 1.1-fold, respectively.

Based on the data from a drug-interaction trial (N=22), the AUC and Cmax of olaparib decreased by 87% and 71%, respectively, when olaparib was administered in combination with rifampicin, a strong CYP3A inducer. Simulations using PBPK models suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC and Cmax of olaparib by 50 - 60% and 20 - 30%, respectively. *In vitro* studies have shown that olaparib is a substrate of Pgp and an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. The

clinical relevance of these findings is unknown. See Appendix B for further discussion.

Storage and stability: All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the IB specifies the appropriate storage.

Preparation and Dispensing:
Olaparib tablets (100 mg or 150 mg tablets) will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain 60 tablets and desiccant. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose. Bottles will be labeled per local regulations.

Administration:
Tablets are to be swallowed whole (not broken, chewed, crushed, dissolved or divided) with water. If given the same time as AZD6738, follow AZD6738 food instructions, otherwise olaparib may be taken with or without food.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that 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.

Availability**:** Supplied by the Astra-Zeneca Pharmaceutical Development R&D Supply Chain

Drug Accountability:
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the olaparib. The drug accountability records should capture drug receipt, drug dispensing, drug return and final disposition.

The investigators will be instructed by the Coordinating Center on the return or destruction of unused olaparib. If any olaparib is lost or damaged, its disposition should be documented in the source documents. Olaparib supplies will be retained at the clinical site pending instructions for disposition by the Coordinating Center.

6.2 **AZD6738**

Description: AZD6738 is a potent ATR inhibitor that is being developed as an oral therapy, both as a monotherapy and in combination with chemotherapy and other anti-cancer agents.

Mechanism of Action: AZD6738 inhibits ATR, which is involved in cell cycle checkpoint regulation, stalled replication fork resolution, single strand break repair (with Replication Protein A) and double strand break repair (with ATR Interacting Protein).

Distribution: AZD6738 has an estimated volume of distribution by modeling of 1 L/kg. The *in vitro* protein binding of AZD6738 at plasma concentrations achieved following planned dosing is approximately 87%.

Metabolism: *In vitro*, CYP3A4 was shown to be the enzyme primarily responsible for the metabolism of AZD6738.

Side effects: The most common adverse events are thrombocytopenia, anemia, neutropenia, nausea, vomiting and fatigue.

Drug Interactions: AZD6738 is metabolized by CYP3A4 and potential inhibits organic anion transporting polypeptide 1B1 (OATP1B1) and P-glycoprotein (Pgp). At clinically relevant doses, it is unlikely to induce CYP1A2, CYP2B6 or CYP3A4. See Appendix B for discussion of management of potential drug interactions.

Storage and stability: All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the IB specifies the appropriate storage.

Preparation and Dispensing:
AZD6738 will be supplied as tablets containing 20 mg, or 80 mg or of drug. AZD6738 tablets will be packed in HDPE bottles with child-resistant closures. Bottles will be labeled per local regulations.

Administration:
AZD6738 tablets are to be swallowed whole (not broken, chewed, crushed, dissolved or divided) with water at the same time as the morning dose of olaparib and with fasting 2 hours prior to dosing and 1 afterwards.

If vomiting occurs shortly after the AZD6738 tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that 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.

Availability**:** Supplied by the Astra-Zeneca Pharmaceutical Development R&D Supply Chain.

Drug Accountability:
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of AZD6738. The drug accountability records should capture drug receipt, drug dispensing, drug return and final disposition.

The investigators will be instructed by the Coordinating Center on the return or destruction of unused AZD6738. If any AZD6738 is lost or damaged, its disposition should be documented in

the source documents. AZD6738 supplies will be retained at the clinical site pending instructions for disposition by the Coordinating Center.

7. COLLECTION OF STUDY VARIABLES

7.1 Recording of Data

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the MSPM during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSPM. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of registration
    - Subject entry into EDC
        - Subject Status
        - Demographics
- During study participation
    - All data should be entered online within 10 business days of data acquisition. Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 7.7 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

7.2 Record Retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents and study-related documents. Records are to be retained and securely stored until the later of: (a) two (2) years following the date a New Drug Application is approved for the Study Drug that is the patient of the Clinical Trial; of (b) two (2) years after the Investigational New Drug Application for such Study Drug is terminated or withdrawn, or such longer period of time as may be required by Participant policies, applicable laws, rule or regulations.

7.3 Data and Safety Monitoring

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by the Rogel Cancer Center Data and Safety Monitoring Committee (DSMC).

The Sponsor Investigator (S-I)/Study Principal Investigator and/or the Project Manager/Delegate will review data and patient safety issues with participating sites per a defined quarterly meeting cadence. Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (SAE reporting, unanticipated problems)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Participating sites are required to ensure all pertinent data for the review period are available in the database at the time of the discussion.

Participating sites unable to participate in the data review meeting are required to provide written confirmation that their site has reviewed the relevant data and patient safety issues for the review period and their site's data are in alignment with the data reported in the database. Written confirmation is to be provided to the Project Manager/Delegate within the timeline requested to retain compliance with monitoring timelines.

Documentation of the teleconference or alternate mechanism utilized to review items above is to be retained in the Trial Master File.

The Project Manager/Delegate is responsible for collating the data from all participating sites and completing the Protocol Specific Data and Safety Monitoring Report (DSMR) form to document the data review meeting discussion.

The DSMR will be signed by the Sponsor-Investigator (S-I)/Study Principal Investigator or designated Co-Investigator and submitted to the DSMC on a quarterly basis for independent review.

7.4 Quality Assurance and Audits

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

7.5 Clinical Monitoring Procedures

Clinical studies coordinated by The University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center of The University of Michigan Rogel Cancer Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo a site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his/her study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate The University of Michigan Rogel Cancer Center personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes Cycle 2. The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

7.6 Efficacy

Response and progression will be evaluated in this study using a combination of the international criteria proposed by the RECIST Committee for measurable disease and the guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG3)[14] for bone metastasis.

Patients will need to be reevaluated for response according to the guidelines below.

7.6.1 PSA

Perform PSA testing at a minimum of 4-weeks intervals with the threshold PSA level at 1.0 ng/mL. To report PSA-based outcomes, PCWG3 recommends that the percent of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment be reported for each patient. PSA rise alone is insufficient to define progression within the study (see Section 7.6.7).

7.6.2 Response evaluation criteria in solid tumors (RECIST)

Response and progression will utilize the new international criteria proposed by the revised RECIST guideline (version 1.1) in combination with other metrics [15]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

7.6.3 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with any drug.

Evaluable for progression-free survival. Only patients who begin treatment will be evaluable for progression-free survival.

Evaluable for objective response. A patient who receives at least one dose of treatment will be considered evaluable for objective response. A patient who does not have an assessment for response after starting treatment will be considered a non-responder and will be censored for progression at the time of removal from the study.

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, begin treatment, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

7.6.4 **Disease parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

> Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

> Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
>
> 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. 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. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

7.6.5 Methods for evaluation of measurable disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

7.6.6 Methods of evaluation of bone disease

Bone disease will be evaluated using Radionuclide bone scan.

7.6.7 Progression/response criteria

Non-lethal disease progression (necessitating discontinuation from trial) is either clinical progression (see Section 7.6.7.5) or radiographic progression based on RECIST (see Section 7.6.7.1, 7.6.7.2) or PCWG3 bone scan criteria (see Section 7.6.7.4). These are combined and

shown in graphical format in Section 7.6.8. Confirmatory bone scan ≥4 weeks after first bone scan progression per PCWG3 is required and must show ≥2 new lesions.

PSA progression alone is NOT sufficient for removal from study.

7.6.7.1 **Evaluation of target lesions**

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

7.6.7.2 **Evaluation of non-target lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be

confirmed at a later time by the review panel (or Principal Investigator).

7.6.7.3 Outcomes based on radionuclide bone scans

The subjectivity in interpreting serial changes in a radionuclide bone scan is well recognized. Thus, the primary outcome will be whether the scan is stable or improved, vs. worse or progression. Changes in intensity will not be used as an outcome measure.

Stable or Improved: A stable or improved classification requires that no new lesions appear at the 3rd cycle (12 weeks) ± 1 week assessments.

Progression (Non-Response): Appearance of **two or more** new skeletal lesions. *An increase in the size or intensity of known skeletal lesions will not be considered progression*. This must be confirmed with another bone scan ≥4 weeks after first bone scan progression per PCWG3 and must show ≥2 new lesions.

7.6.7.4 Outcomes based on post-therapy PSA changes

These definitions are intended to characterize the PSA changes on study for the purpose of reporting of results. PSA progression is NOT criteria to remove from study.

Complete Response (CR): Undetectable PSA (≤0.2 ng/ml) that is confirmed by another PSA level at no less than 4 weeks interval.

Partial Response (PR): Decrease in PSA value by ≥ 50% that is confirmed by another PSA level at no less than 4 weeks interval.

Stabilization (SD): Patients who do not meet the criteria for PR or PD for at least 90 days on study (2 cycles of treatment) will be considered stable

Progression (PD): 25% increase over baseline or nadir whichever is lower and an increase in the absolute value of PSA level by 2 ng/ml that is confirmed by another PSA level at no less than 4 weeks interval.

7.6.7.5 Definition of progression based on pain

Progression by pain criteria is based on pain due to prostate cancer requiring one or more of the following palliative interventions:

- Opioid Therapy: Intravenous, intramuscular or subcutaneous opioid therapy administered as a single dose; oral or transdermal opioid analgesic use administered for 10 out of 14 consecutive days, and/or requiring Radionuclide or Radiation therapy.
- Evidence of disease at the site of pain is required. Pain requiring only non-opioid analgesics will not be considered disease progression.

7.6.7.6 Progression-free survival

PFS is defined as the duration of time from date of assignment to treatment arm to time of objective progression or death, whichever occurs first (see Section 10.1).

7.6.8 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 progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

TABLE 5 Best Overall Response For Patients with Measurable Disease (i.e. Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration*." Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 6 Best Overall Response for Patients with Non -Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes of No	PD
Any	Yes	PD

** 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is confusing.*

7.6.9 Duration of combined radiographic and PSA response

Duration of combined radiographic and PSA response is measured from the time of first documented response (RECIST v1.1 CR/PR or PSA decline ≥50%) until death, recurrent or progressive disease (based on RECIST v1.1) or first PSA increase ≥25% and ≥ 2 ng/ml above the PSA nadir.

7.7 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

7.7.1 Adverse event reporting requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment administration through 30 days after the last dose of study treatment. Any serious adverse event that occurs more than 30 days after the last study treatment and is considered related to the study treatment will be reported to sponsor investigator. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.
Any medical condition or laboratory abnormality with an onset date before initial study treatment is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.
All events meeting the criteria and definition of an AE or SAE, as defined in this section, occurring from the initial study treatment through 30 days following the last dose of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment. In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event.

Adverse events after the 30 day follow up period

For Pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. After study completion, vigilance will be maintained by either an a) annual

chart review for the diagnosis or b) phone call asking the patient whether they have been diagnosed with MDS/AML or a new malignancy (one of these should happen between months 10-12 after discontinuation). If a patient has been diagnosed with MDS/AML or another malignancy, a questionnaire may be sent to them for further information. This will continue for 5 years after a patient completes study.

At any time after a patient has completed the study, if an Investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify the Principal Investigator who will notify AstraZeneca, Patient Safety.

7.7.2 Definition of adverse events

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.
- Symptoms of prostate cancer are not to be considered adverse events for this study. The following symptoms are indicative of underlying disease and will not be reported as adverse events (unless the event is considered serious): bone pain, urinary frequency, hesitancy or urgency.
- Abnormal laboratory values or test results constitute adverse events if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms or diagnoses associated with them.

7.7.3 AZD6738 adverse events of special interest

There are no AESI for AZD6738 which require additional data collection.

7.7.4 Olaparib adverse events of special interest:

Adverse events of special interest [AESI] are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a questionnaire to help characterize the event and gain a better understanding regarding the relationship between the event and study treatment.

7.7.5 **Definitions of serious adverse event**

An adverse event is considered "serious" if, in the view of either the investigator or Sponsor-Investigator, it results in any of the following outcomes:

- Death

  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event

  An adverse even is considered 'life-threatening' if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for > 24 hours.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Adverse events for malignant tumors reported during a study should generally be assessed as serious AEs. If no other seriousness criteria apply, the important medical event criterion should be used. Medical judgment on an individual event basis should be applied to clarify if non-serious AE or not. Please contact PI if this occurs for guidance.
- Important medical event

  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE. The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

7.7.6 Expected adverse events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.

7.7.7 Unexpected adverse events

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in the protocol, or in the informed consent document

7.7.8 Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction is when an SAE occurs that is unexpected in the nature and/or severity compared with the information set out in Investigators Brochures.

7.7.9 Adverse event characteristics

7.7.9.1 CTCAE term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

7.7.9.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.
Definite – The AE is clearly related to the study treatment].
Probable – The AE is likely related to the study treatment].
Possible – The AE may be related to the study treatment.
Unlikely – The AE is doubtfully related to the study treatment.
Unrelated – The AE is clearly NOT related to the study treatment.

7.7.10 Reporting of serious adverse events

7.7.10.1 Reporting procedures for multi-site trials

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study drug, will be reported to the Principal Investigator and also to the Coordinating Center. All SAEs and UPs must be reported to the Coordinating Center within 24 hours of first awareness of the event. Events should be reported using the Coordinating Center's SAE form as available in the study database. A copy of the SAE form as available in the study database should be sent to the Coordinating Center via fax at 734-232-0744 or via email to CTSU-Oncology-Multisite@med.umich.edu within 24 hours of the site's knowledge of the event.

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

All SAEs and UPs will be reported to the IRB per current institutional standards.
The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study drug.

7.7.10.2 **Reporting procedures to AstraZeneca**

All Serious Adverse Events (SAEs) occurring from the initial study treatment administration through 30 days following the last dose of the study treatment will be reported by the Coordinating Center to AstraZeneca. Any SAEs occurring after 30 days following the last dose of the study treatment that are believed to be related to study drug will also be reported to AstraZeneca.

For pharmacovigilance purposes and characterization, any case of MDS/AML or new primary malignancy occurring after 30 day follow up period should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE [e.g. non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases. If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and/or post study completion then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe. Otherwise, after study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients.
The Coordinating Center will send the initial completed SAE Form within 24 hours of receipt via email to AEMailboxClinicalTrialTCS@astrazeneca.com.

If only limited information is initially available or an ongoing SAE changes in its intensity or relationship to the study drug, or if new information becomes available, a follow-up report will be generated and sent to AstraZeneca within 24 hours of receipt.

7.7.10.3 **Reporting procedures to FDA**

In this trial, serious, unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the Food and Drug Administration via the MedWatch 3500A. The Michigan IND/IDE Assistance Program (MIAP) will be responsible for reporting SAEs to the FDA that meet the reporting requirements in 21 CFR 312.32.

A copy of the MedWatch report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.
* A cover page should accompany the MedWatch form indicating the following:
- External Scientific Research (ESR)
- The investigator IND number assigned by the FDA
- The investigator's name and address

- The trial name/title and AstraZeneca ESR reference number

* Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.
* Send SAE report and accompanying cover page by way of Email to AEMailboxClinicalTrialTCS@astrazeneca.com

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA

7.7.11 Routine reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

7.7.12 Reporting of unanticipated problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.
Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the Coordinating Center within 24 hours of the study team becoming aware of the problem.

7.7.13 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 6 months *after the last dose* should be followed up and documented.

Sites should notify the Coordinating Center for any patient partner pregnancies within 24 hours of knowledge of the pregnancy.

7.7.14 Genetics

As this study entails biopsy or circulating tumor genetic analysis at enrollment (unless already completed), genetic data will be analyzed and housed. The exploratory correlatives also will capture similar information.

7.7.15 Circulating correlative analytes

These will be collected per study calendar and are encoded to protect privacy

7.7.16 Specimen banking

Patient excess samples collected within this study (peripheral blood and excess tissue from biopsy returned from TEMPUS) will be retained at University of Michigan if the patient consented to specimen banking. Specimens will be stored indefinitely or until they are used up. If future use is withdrawn by the patient, best efforts will be made to stop any additional studies and destroy the previously obtained specimens.
Specimens being stored long-term for potential use not outlined in the protocol are subject to University of Michigan Policies Governing Tissue Sample Collection.
If a patient consented to the analysis of prior obtained tissue (e.g. prior biopsies before enrolment in study), they may be requested and housed at the University of Michigan.

7.7.17 Specimen management with AstraZeneca

As rarer subgroups are being identified in prostate cancer, the need to combine anonymized results across studies using the same analytical process is important. To minimize genetic exposure risks, any tissue shared will NOT be allowed to undergo large-scale (>30 genes) next generation sequencing. Again, patients may opt-out of sharing any tissue with AstraZeneca.

8. ROLES AND RESPONSIBILITIES

8.1 Sponsor Investigator

The Sponsor Investigator is responsible for performing the following tasks:

- Responsibility for the overall conduct of the study at all participating sites and for monitoring the progress of the study
- Reviewing and ensuring reporting of SAEs
- Reviewing data from all participating sites

8.2 Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, guidelines consistent with good clinical practice (GCP), and applicable Standard Operating Procedures (SOPs). Registering all patients

with the coordinating center by submitting the eligibility checklist, supporting source documentation, and signed informed consent promptly
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol
- Maintaining regulatory binders on site and providing copies of all required documents to the coordinating center
- Collecting and submitting data according to the schedule specified by the protocol
- Responding to queries in a timely manner

8.3 Coordinating Center

The Coordinating Center is responsible for performing the following tasks:
- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals and required regulatory documents from each site.
- Managing patient registration
- Developing and maintaining Clinical Data Management documents and procedures
- EDC development, setup of study database, and subsequent design changes
- Participating in review of content of the EDC against the protocol requirements
- EDC system administration (user/site accounts setup, maintenance and revocation)
- Data review, cleaning, query management and resolution
- Establishing procedures for documentation, reporting and submitting of AEs and SAEs.
- Reviewing SAEs
- Training participating sites on EDC
- Collecting and compiling data from each participating site
- Data reviewing from all participating sites
- Facilitating monitoring visits by securing selected source documents and research records from participating sites for review, or by monitoring at participating sites.

9. ETHICAL AND REGULATORY REQUIREMENTS

9.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements

9.2 Subject Data Protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's

identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

9.3 Informed Consent

Before obtaining consent, members of the study team will review the rationale for the treatment program with the patient. The discussion will review the alternatives available (including hormonal therapy, chemotherapy, or supportive care as appropriate), the potential benefits of this program, the risks and the probability of their occurrence, and the procedures to minimize these risks. Should an AE occur, the provisions available to ensure medical intervention will also be reviewed. Why the risks are reasonable in relation to the anticipated benefits, incentives, or costs that will or may be incurred as a result of participating in the study, as well as the efforts to maintain confidentiality, will also be discussed with the patient.

Patients will be required to sign and date an informed consent form that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the IRB. The medical record will include a statement that written informed consent was obtained (and document the date that it was obtained) before the patient is enrolled in the study. The original signed document will become part of the patient's medical record, a copy will be forwarded to the lead site/sponsor pursuant to sponsor registration and a copy will be sent home with each patient.

The consent form will include the following:

- the nature and objectives, potential toxicities, and benefits of the intended study
- the length of therapy and likely follow-up required
- alternatives to the proposed therapy (including available standard and investigational therapies)
- the name of the investigator(s) responsible for the protocol
- the right of the patient to accept or refuse treatment and to withdraw from participation in this study

9.4 Changes to the Protocol and Informed Consent Form

Before starting the study, the protocol must be approved by each institution's IRB or Independent Ethics committee (IEC). Amendments to the protocol may be made only with consent of the lead site/sponsor and are pending until approval by IRB before instating.

9.5 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. After this discussion, they will be asked to sign a Notice of Privacy Practice research authorization/HIPAA form. The original signed documents will become part of the patient's medical records, and each patient will receive a copy of the signed documents. The use and disclosure of protected health information will be limited to the individuals described in the research authorization form. The research authorization form must be completed by the principal investigator and approved by the IRB.

9.6 Terminating or Modifying the Study

AE and laboratory data from this trial will be assessed by the lead site on an ongoing basis. SAEs will be reviewed as they are reported to the lead site, and the medical monitor will make an assessment regarding the safety of continuing or modifying the study. The futility evaluation after 17 patients as described. This assessment will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the lead site/sponsor or the principal investigator be that the study should be terminated, the study will be closed to further accrual. Patients who are receiving intervention will be assessed individually by the investigator to see if it is in the patients' best interest to continue, which might be the case for a patient that is responding to the intervention. Follow-up safety assessments will be performed for all patients who are terminated from the study prematurely.

10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

10.1 Study Endpoints

10.1.1 Analysis of the primary endpoint

The primary endpoint of the study is the response rate of the DRPro cohort. Response is defined as achieving a complete response (CR) or partial response (PR) by either radiographic response according to RECIST v 1.1 or PSA response. The count of responses and corresponding response rate with the 95% binomial confidence interval will be reported in the DRPro patients.

10.1.2 Analysis of the secondary endpoints

- The response rate and 95% binomial confidence interval will be reported for DRDef patients.

The following endpoints will be reported for DRDef and DRPro patients separately

- Objective progression-free survival (combined radiographic and clinical progression-free survival) will be reported using Kaplan-Meier methods. This is measured from the date of treatment arm assignment until the specified tumor progression (assigned at the earliest observed time). Patients whose disease has not progressed at follow-up will be censored at the date when the last tumor assessment determined a lack of progression.
- Objective radiographic disease response rate is determined by the proportion of patients with measurable disease that have a response (CR+PR) according to RECIST v1.1. The proportion of responders will be reported with the corresponding 95% binomial confidence interval.
- PSA progression-free survival (PSA-PFS) will be reported as the composite of survival and duration of PSA control as defined by after a start of therapy from baseline to time of first PSA increase ≥25% and ≥2 ng/mL above the nadir and confirmed by a second value at or beyond 4 weeks later. Kaplan-Meier methods will be used to report PSA-PFS.

- PSA response rate (≤ 0.2 ng/ml, 50% decline, 90% decline) proportions will be reported with corresponding 95% binomial confidence intervals. A waterfall plot of the best PSA response decline will be reported.
- Evaluate the qualitative and quantitative AE summaries will be reported by DNA repair status and organized by body system, frequency of occurrence, intensity (e.g. severity grade) and causality or attribution. Counts and proportions will be included. Treatment exposure will be summarized for all patients, including dose administration, number of cycles, dose modifications or delays and duration of therapy. Categorical variables will be reported using counts and frequencies. Continuous variables will be summarized using means or medians with the appropriate measure of variability.
- Duration of combined radiographic and PSA response will be reported using Kaplan-Meier methods.

10.1.3 Correlative objectives

To evaluate the predictive capacity of circulating analytes within both genetic cohorts circulating tumor DNA sequencing/quantification, circulating tumor cell number, circulating tumor cell composite gene expression by pooled RT-PCR will be measured. Continuous biomarkers will be described using means and standard deviations or medians with percentile. Categorical covariates will be described with counts and frequencies.

- The association of correlative biomarkers with response will be assessed using logistic models with response as outcome and the correlative covariates as the independent predictors. The association of correlative biomarkers with failure will be assessed using Cox models with response rate as the outcome and correlative covariates as the independent predictors
- Correlations between the metastatic biopsy and circulating analysis will be compared and the proportion of matches will be reported. McNemar's test may be used.
- Correlations of liquid assays and tissue-based analyses will be reported using Pearson or Spearman correlation coefficients as is appropriate.

10.2 Analysis Populations

10.2.1 Response-to-treatment populations

All patients who meet eligibility criteria and receive at least one dose of study medication will be included in the main analysis of the response rate, even if there are major protocol deviations (e.g., incorrect treatment schedule or drug administration). Each patient will be assigned to one of the following categories for each response outcome:

TABLE 7: Categories for Response to Treatment

Category	Response
1	Complete response
2	Partial response
3	Stable disease
4	Progressive disease
5	Early death from malignant disease
6	Early death from toxicity
7	Early death from other causes

8	Unknown (not assessable/insufficient data)

NOTE: By arbitrary convention, category 8 designates unknown status in a clinical database. Patients in response categories 4 to 8 will be considered to have treatment failure (disease progression)

Conclusions are to be based on the population of all eligible patients who receive at least one dose of study medication. Subanalyses will be performed on various subsets of patients, such as those with no major protocol deviations, those who have at least one measure of response after starting treatment or those who continued in the study for the entire treatment period (i.e. did not withdraw prematurely). Sub-analysis will not serve as the basis for drawing conclusions concerning treatment's efficacy.

10.2.2 Safety population

All patients enrolled in the study who receive at least one dose of study treatment will be included in the safety analysis population and considered evaluable for toxicity and safety from the time of their first dose. Analysis will be completed by treatment received rather than treatment assigned. Demographic and baseline characteristics for the safety population will be summarized by number and percent for categorical data (e.g., race/ethnicity) and by descriptive statistics for continuous data (e.g., weight, vital signs, EKG readings, disease status).

10.3 Safety Analysis

10.3.1 Evaluation of adverse events

Treatment-emergent AEs will be translated from investigator terms to a custom medical dictionary and summarized (number and percentage of patients) for each treatment arm for all patients who receive at least one dose. AE summaries will be reported by arm and organized by body system, frequency of occurrence, intensity (i.e., severity grade), and causality or attribution. Patients who experience an AE more than once will be counted only once. The occurrence with the maximum severity will be used to calculate intensity.

10.3.2 Evaluation of serious adverse events and premature withdrawals

AEs deemed serious and those resulting in treatment withdrawal or death will be summarized separately. Narrative paragraphs will be generated to describe the circumstances surrounding each SAE and death.

10.3.3 Extent of exposure

Treatment exposure will be summarized for all patients, including dose administration, number of cycles, dose modifications or delays, and duration of therapy. This will be reported separately by treatment arm.

10.3.4 Early stopping

Stopping rules for excessive toxicity will be incorporated for patients. Excessive toxicity will be defined as removal from treatment due to toxicity despite dose modification. We consider excessive toxicity if more than 25% of subjects have to stop the trial because of toxicity. Once 10 subjects have been enrolled, we will continually monitor the rate of toxicity withdrawal and stop if we have evidence that the rate is above 25%. If the rate is >25% at any time after 10

patients are accrued, enrollment will be halted and re-evaluated for dose reduction or closed to accrual.

10.3.5 Statistical procedures

Summary statistics include the number of observations, mean, standard deviation, median, minimum, and maximum values. As this is not a comparative trial, p-values will be used sparingly.

10.3.6 Sample size calculation

The statistical design for DRPro will be an Optimal Simon 2-stage Phase II. Based on the TOPARP-A study the null response rate for DRPro is 6% and a response rate of 6% or less would not be interesting. Accrual of 35 DRPro patients will provide 80% power to detect a response rate of 20% or greater with 5% type I error. Stage 1 will accrue 17 DRPro patients. If 1 or less DRPro patients have a preliminary response (CR/PR using radiographic by RECIST v.1.1 or PSA decline ≥50%) then the DRPro cohort will stop. If 2 or more responses occur, then the 2nd stage will begin and another 18 DRPro patients will be accrued. If 5 or more patient responses are seen out of the 35 DRPro patients, then the combination treatment will be deemed interesting for further study in the DRPro population.

The statistical design for the DRDef is a Mini-Max Simon 2-stage Phase II. Based on a response rate of 45% within the first 12 weeks in TOPARP-A, a response rate of under 45% would not be interesting. Stage 1 of this design requires 12 DRDef patients and if 5 or less patients have a preliminary response (CR/PR using radiographic by RECIST v.1.1. or PSA decline ≥50%), then the DRDef cohort would not be of interest. If 6 or more patients do respond, this would support consideration to expand (with amendment or new protocol) with another 13 patients (to a total of 25 patients) or a completely separate trial. Accrual of 25 patients would provide 80% power to detect a response rate of 70% or greater with 5% type I error. If 16 or more patient responses were seen in a 25 total DRDef patient cohort, then the combination treatment would be deemed interesting for further study DRDef . Different RR are used for DRDef and DRPro as different expected baseline RR.

10.3.7 Derived variables

- Change from baseline will be calculated as the rating after baseline minus the rating at baseline
- Percent change from baseline will be calculated as the rating after baseline minus the rating at baseline quantity divided by the baseline.
- Duration of treatment will be defined as the number of days from the first day of protocol assigned intervention to the last day of protocol treatment. If the last day of protocol treatment is missing, the date of the last visit will be substituted for the missing value

10.4 Data Monitoring Committee

The trial will utilize the University of Michigan Rogel Cancer Center's Data Monitoring Committee to monitor this study. The University of Michigan Rogel Cancer Center will also compile the relevant data from participating sites.

11. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED

11.1 Overdose

There is currently no specific treatment in the event of overdose with AZD6738 and possible symptoms of overdose are not established.

AZD6738 must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 160 mg by mouth daily for 7 out of 28 days for AZD6738 and 300 mg by mouth twice a day for olaparib.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established. *Olaparib* must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 300 mg twice daily (tablet).

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel should inform the Coordinating Center **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it. The Coordinating Center will send the information within 24 hours of receipt to AstraZeneca Patient Safety.
The designated AstraZeneca representative works with the Coordinating Center to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 7.7. For other overdoses, reporting should be done within 30 days.

11.2 Paternal Exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 6 months *after the last dose* should be followed up and documented.

12. LIST OF REFERENCES

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer Statistics, 2017.* CA Cancer J Clin, 2017. **67**(1): p. 7-30.
2. Robinson, D., et al., *Integrative clinical genomics of advanced prostate cancer.* Cell, 2015. **161**(5): p. 1215-28.
3. Mateo, J., et al., *DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer.* N Engl J Med, 2015. **373**(18): p. 1697-708.
4. Hussain, M., et al., *Targeting Androgen Receptor and DNA Repair in Metastatic Castration-Resistant Prostate Cancer: Results From NCI 9012.* J Clin Oncol, 2017: p. Jco2017757310.
5. Cheng, H.H., et al., *Biallelic Inactivation of BRCA2 in Platinum-sensitive Metastatic Castration-resistant Prostate Cancer.* Eur Urol, 2015.
6. Balmana, J., et al., *Phase I trial of olaparib in combination with cisplatin for the treatment of patients with advanced breast, ovarian and other solid tumors.* Ann Oncol, 2014. **25**(8): p. 1656-63.
7. Rajan, A., et al., *A phase I combination study of olaparib with cisplatin and gemcitabine in adults with solid tumors.* Clin Cancer Res, 2012. **18**(8): p. 2344-51.
8. Oza, A.M., et al., *Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial.* Lancet Oncol, 2015. **16**(1): p. 87-97.
9. Wilson, R.H., et al., *A phase I study of intravenous and oral rucaparib in combination with chemotherapy in patients with advanced solid tumours.* Br J Cancer, 2017. **116**(7): p. 884-892.
10. Pujade-Lauraine, E., et al., *Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial.* Lancet Oncol, 2017. **18**(9): p. 1274-1284.
11. Kaufman, B., et al., *Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation.* J Clin Oncol, 2015. **33**(3): p. 244-50.
12. Robson, M., et al., *Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation.* N Engl J Med, 2017. **377**(6): p. 523-533.
13. Krebs, M.e.a., *Phase I Study of AZD6738, an inhibitor of ataxia telangiectasia Rad3 related (ATR), in combination with olaparib or durvalumab in patients with advanced solid cancer.* AACR annual meeting 2018. **Abstract CT026**.
14. Scher, H.I., et al., *Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3.* J Clin Oncol, 2016. **34**(12): p. 1402-18.

15. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

13. APPENDICES

Appendix A: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Appendix B: Guidelines Regarding Potential Interactions with Concomitant Medications

Appendix C: Acceptable Birth Control Methods

Appendix D: Genomics Research

Appendix E: Study Management During COVID-19

Appendix A Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 5.4.10 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment
- Notify the Company within 1 day of PHL criteria being met as SAE under serious criteria "important medical event" and causality according to CSP process for SAE reporting.
- For patients meeting PHL criteria prior to starting investigational drugs, the investigator is not required to submit a PHL SAE unless there is a significant change in patient's condition

The Company contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Company. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>
- Complete the three Liver CRF Modules as information becomes available

Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met. No later than 3 weeks after the biochemistry abnormality was initially detected, the Company contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The Sponsor Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.
Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now ' Hy's Law Case') ensuring causality assessment is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the previously submitted PHL SAE report following CSP process for SAE reporting according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined
-

<u>Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment</u>

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment. At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required

- If there is a significant change notify the Sponsor representative, who will inform the Company, then follow the subsequent process described in Potential Hy's Law Criteria met of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Company if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.
The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.
The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?

If No: follow the process described in Potential Hy's Law Criteria met of this Appendix

If Yes:
Determine if there has been a significant change in the patient's condition# compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 5.4.10

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Company if there is any uncertainty.

References

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix B Guidelines Regarding Potential Interactions with Concomitant Medications

AZD6738 is an investigational drug for which no data on *in vivo* interactions are currently available. Potential interaction is considered on the basis of preclinical *in vitro* data only. The lists of CYP and transporter inhibitors/inducers, and CYP and transporter substrates are available in this appendix. They are not exhaustive and the absence of a drug from these lists does not imply that its combination with AZD6738 is safe. If AZD6738 is being administered in combination, potential interactions of the combination partner should also be considered.

Restrictions regarding drugs affection CYP3A metabolism

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and AZD6738; a potential interaction is considered on the basis of preclinical and *in vitro* data only. AZD6738 is predominantly eliminated via CYP3A metabolism (approximately 60%), therefore CYP3A inhibitors or inducers may increase or decrease exposure to AZD6738, respectively. Potent inhibitors or inducers of CYP3A should not be combined with AZD6738.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP3A activity. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

TABLE 8: Drugs Known to be Inhibitors and inducers of CYP3A - manage by stopping/not using these medications

Potent CYP3A inhibitors		Potent CYP3A inducers
boceprevir	nefazodone	avasimibe
clarithromycin	nelfinavir	**carbamazepine**
conivaptan	**posaconazole**	enzalutamide
elvitegravir/ ritonavir	ritonavir	mitotane
fluconazole	saquinavir	**phenobarbital**
grapefruit juice[a]	telaprevir	**phenytoin**
indinavir	telithromycin	rifabutin
itraconazole	tipranavir/RIT	rifampin
ketoconazole	troleandomycin	**St John's Wort**
lopinavir/ RIT	**voriconazole**	
mibefradil		

List created using the University of Washington Drug-Drug Interaction Database January 2013.

RIT = Ritonavir.

Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity

a. Double-strength grapefruit juice

Patients should abstain from eating grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) while on olaparib and AZD6738 therapy.

Drugs known to be inhibitors or inducers of Pgp and/or BCRP, undertake appropriate monitoring if co-administration is necessary

AZD6738 is a substrate of Pgp and BCRP. Co-administration of Pgp inhibitors/inducers or BCRP inhibitors/inducers may affect exposure to AZD6738 therefore it is recommended that these are not co-administered with AZD6738.
These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate Pgp activity or BCRP activity. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 9: Drugs known to be inhibitors or inducers of Pgp
- manage by stopping/not using these medications

Drugs Known to be Inhibitors of Pgp[a]		**Drugs Known to be Inducers of Pgp[b]**
Amiodarone	mirabegron	avasimibe
azithromycin	nelfinavir	**carbamazepine**
captopril	**nifedipine**	efavirenz
carvedilol	nitrendipine	genistein
clarithromycin	**paroxetine**	phenytoin
conivaptan	quercetin	rifampin
cremophor	quinidine	**St Johns Wort**
curcumin	ranolazine	
diltiazem	rifampin	
dronedarone	ritonavir	
elacridar	saquinavir/ritonavir	
erythromycin	schisandra chinensis	
felodipine	extract	
fluvoxamine	**St Johns Wort**	
ginkgo	talinolol	
indinavir	telaprevir	
itraconazole	telmisartan	
ketoconazole	ticagrelor	
lapatinib	tipranavir/ritonavir	
lopinavir and ritonavir	tolvaptan	
mibefradil	valspodar (PSC 833)	
milk thistle	**verapamil**	

a. Inhibitors listed for Pgp are those that showed >25% increase in exposure to a Pgp substrate (e.g. digoxin).

b. Inducers listed for Pgp are those that showed >20 % decrease in exposure to a Pgp substrate (e.g. digoxin)

Table 10: Drugs known to be inhibitors or inducers of BCRP
- manage by stopping/not using these medications

Drugs Known to be Inhibitors of BCRP		Drugs Known to be inducers of BCRP
Afatinib	Regorafenib	Please check individual drugs on a case by case basis
Aripiprazole	Rilpivirine	
Curcumin	Sulfasalazine	
Cyclosporine	Sunitinib	
Elacridar	Tacrolimus	
Erlotinib	Teriflunomide	
Fluvastatin	Trametinib	
Fumitremorgin	Trifluoperazine	
Gefitinib	Vismodegib	
Ivermectin	eltrombopag	
Lapatinib	Atazanavir	
Nilotinib	Lopinavir	
Novobiocin	Ritonavir	
Pantoprazole	Tipranavir	
Pitavastatin	**Omeprazole**	
Ponatinib	Estrone	
Quercetin	17b-estradiol	
Quizartinib	Imatinib mesylate	
Rabeprazole		

List created using http://dmd.aspetjournals.org/content/dmd/43/4/490.full.pdf

Note: Although BCRP is involved in a number of clinically relevant DDIs, none of the cited inhibitors above is truly specific for this transporter

Drugs known to be substrates of CYP3A4 and/or CYP2B6, undertake appropriate monitoring if co-administration is necessary

AZD6738 is a potential inducer of CYP3A4 and CYP2B6. Therefore, caution should be applied with co administration of drugs that are either completely metabolized by CYP3A4 and/or CYP2B6, or that are substrates of CYP3A4 and/or CYP2B6 and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolized by CYP3A4 and/or CYP2B6 may be reduced.

Table 11: Drugs known to be metabolized by CYP3A4 and have a narrow therapeutic index
- may co-administer, monitor toxicity/levels more frequently if possible

Alfentanil	Quinidine
Cyclosporine	Sirolimus
Dihydroergotamine	**Tacrolimus**
Ergotamine	Astemizole
Fentanyl	Cisapride
Pimozide	Terfenadine

Table 12: Drugs known to be metabolized by CYP2B6 and have a narrow therapeutic index
- may co-administer, monitor for toxicity and check levels more frequently if possible

Cyclophosphoamide	**methadone**
Ifosfamide	methoxetamine
Efavirenz	nevirapine
Bupropion	propofol
Propofol	selegiline
Thiotepa	**sertraline**
Sorafenib	sorafenib
alfentanil	tamoxifen
ketamine	**valproic acid**

From Flockhart DA (2007). "Drug Interactions: Cytochrome P450 Drug Interaction Table". Indiana University School of Medicine

Drugs known to be substrates of OATP1B1 and BCRP, undertake appropriate monitoring if co-administration is necessary

AZD6738 is also an inhibitor of OATP1B1 and BCRP. Caution should be applied with co-administration of substrates of OATP1B1 and/or BCRP as AZD6738 may increase their exposure.

These lists are not intended to be exhaustive and appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 13: Drugs known to be substrates of OATP1B1
- may co-administer, be aware of potential drug toxicity

Atorvastatin	Methotrexate
Fluvastatin	Rifampin
Lovastatin	Bosentan
Pitavastatin	**Glyburide**
Pravastatin	Repaglinide
Rosuvastatin	**Valsartan**
Simvastatin	Olmesartan
Ezemibe	Atrasentan

List created using https://www.solvobiotech.com/transporters/OATP1B1

Table 14: Drugs known to be substrates of BCRP
- may co-administer, be aware of potential drug toxicity

Anthracyclines	Mitoxantrone
Daunorubicin	nucleoside analogs
Doxorubicin	prazosin
Topotecan	**pantoprazole**
SN-38	topotecan
Irinotecan	**rosuvastatin and other statins**
Methotrexate	teriflunomide
Imatinib	**chlorothiazide**
Irinotecan	

List created using https://www.solvobiotech.com/transporters/bcrp

Olaparib:

This is guidance on management of olaparib on study when a strong or moderate CYP3A must be used for a short time.

If a strong CYP3A inhibitor must be used, olaparib should be dose reduced to 100 mg daily for the duration of concomitant therapy and for 5 half-lives afterwards. If a moderate CYP3A inhibitor must be used, olaparib should be reduced to 150 mg po twice a day for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards. After washout, olaparib may be increased to full prior dose.

Appendix C Acceptable Birth Control Methods

Olaparib is regarded as a compound with medium/high fetal risk.

Subjects who are sexually active, must agree to use TWO highly effective forms of contraception in combination (as listed below). This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 6 months after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).
Patients must use a condom during treatment and for 6 months after the last dose of study drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception if they are of childbearing potential (as listed below) with two forms of contraception. Male patients should not donate sperm throughout the period of taking study drug(s) and for 6 months following the last dose of study drug(s). Men must not donate sperm throughout the period of taking study drug(s) and for 6 months after the last dose of study drug.

Acceptable non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the study and for at least 6 months after the last dose of study drug (for 6 months after last dose for male patients. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods or declaration of abstinence solely for the duration of a study) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine device PLUS male condom. Provided coils are copper-banded

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (e.g. Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g. Implanon, Norplant) PLUS male condom
- Norelgestromin / ethinyl estradiol transdermal system PLUS male condom
- Intrauterine system (IUS) device (eg, levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g. ethinyl estradiol and etonogestrel) PLUS male condom

Appendix D: Genomics Research

Background and Rationale

This trial requires analysis of the genetic content of cancer cells or circulating DNA. This is imperative to the successful execution of the trial and is required. Germline and tumoral analysis will be completed if possible to truly isolate the somatic vs inherited genetic components of each individual cancer. These results will be shared with the patient and appropriate referrals completed if necessary. See laboratory manual for how samples are collected and study calendar for when they are collected.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 25 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
For all samples irrespective of the type of coding used the DNA will be extracted from the blood, saliva or tissue. The sample will utilize only the patient ID, which the master key is kept securely. The samples and data for genetic analysis in this study will be single coded. The link between the subject enrollment/registration code and the DNA number will be maintained and stored in a secure environment, with restricted access. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.