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Olaparib in Prostate Cancer Patients With Evidence of Homologous Recombination Deficiency As Assessed Using an Integrated Genomic Signature

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1.0 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Schedule of Activities

	Pre-Screening	**Screening**	**Treatment Cycles[a]**					**End of Treatment**
Treatment Cycle	**Pre-Screening**	**Screening**	**Cycle 1[g]**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**After Cycle 4**	**Discontinue[h]**
Cycle Day		**Day -30 to 0**	**Day 1 +/- 7 days**	**Day 1 +/- 7 days**	**Day 1 +/- 7 days**	**Day 1 +/- 7 days**	**Day 1 +/- 7 days**	**Within 30 days**
Administrative Procedures								
Informed Consent		X						
Inclusion/Exclusion Criteria		X						
Demographics and Medical History		X						
Prior and Concomitant Medication Review		X	X	X	X	X	Q1C	X
Olaparib Dispensation			X	X	X	X	Q1C	
Clinical Assessments								
Review Adverse Events			X	X	X	X	Q1C	X
ECOG Performance Status		X	X	X	X	X	Q1C	X
Vital Signs and Weight		X	X	X	X	X	Q1C	X
Physical Examination[b]		X	X	X	X	X	Q1C	X

EKG		X						
Laboratory Assessments								
LOH Assessment	X[d]							
iHRD Analysis/Whole Exome Sequencing		X						
PSA		X	X			X	Q3C	X
Testosterone Level		X						
CBC with Differential		X	X	X	X	X	Q1C	X
Comprehensive Serum Chemistry Panel		X	X	X	X	X	Q1C	X
PT/INR and PTT		X						
Urinalysis		X						
Correlative Studies Blood Collection[c]			X			X		X
Research Biopsy[e]		X						X
Radiographic Assessments[f]		X[i]				X	Q3C	

A. One treatment cycle is equal to 28 days
B. Full physical exam is required at screening. Subsequent physical exams may be targeted.
C. Refer to Laboratory Manual for details on correlative blood sample processing.
D. Pathologic assessment to evaluate LOH score is a pre-screening requirement and will be performed on archival tissue or ctDNA. Sufficient tissue must also be available for whole exome sequencing in order to determine iHRD status.
E. If archival metastatic tissue previously obtained is already available and suitable for research assessments, another metastatic biopsy will not be mandated. Research biopsy will only occur if considered safe and feasible by the treatment team. CBC with Differential, PT/INR and PTT will only be obtained in the pre-screening period if metastatic biopsy is planned.
F. Radiographic assessments should include a CT chest/abdomen/pelvis and bone scan. PET/CT or MRI may be used as initial screening assessments.
G. Assessments done during the screening period do not need to be repeated if within 7 days.
H. Assessments do not need to be repeated if within 7 days
I. Radiographic assessments do not need to be repeated if within 8 weeks

1.2 Synopsis

Protocol Title: Olaparib in Prostate Cancer Patients With Evidence of Homologous Recombination Deficiency As Assessed Using an Integrated Genomic Signature

Short Title: Novel Genomic Signature and Olaparib Response

Rationale:

Homologous recombination repair (HRR) is a key pathway involved in resolving double-stranded DNA (dsDNA) breaks. Inactivating mutations in homologous recombination (HR) genes have been associated with improved outcomes to PARP inhibitors (PARPi) in men with mCRPC. Our group has developed an integrated approach to calling HRD signatures (iHRD - integrated Homologous Recombination Deficiency) with the goal of predicting sensitivity to DNA damaging therapeutics such as PARPi. This signature is a multiparametric classification that was defined using 418 patient samples from the Stand Up 2 Cancer (SU2C) repository and was subsequently validated on a set of 139 tumors from our UW rapid autopsy program. Importantly, this assay allows us to identify *11-12% of mCRPC patients who do not have mutations in HR genes but who we would predict to have functional loss of HR and therefore stand to benefit from PARP inhibition.* Based on these observations, we *hypothesize that iHRD signature analysis will allow us to identify more men who are likely to benefit from PARP inhibitors, including those (11-12% of mCRPC population) who are otherwise excluded from clinical trials evaluating these agents.* We therefore plan to conduct a Phase II study to evaluate the utility of using iHRD signature analysis to select patients for treatment with olaparib.

Objectives and Endpoints:

Primary Objective:

Determine the percent of patients achieving a ≥50% reduction in PSA (PSA50 response) following at least 12 weeks of treatment with olaparib 300mg twice daily in men with metastatic castration-resistant prostate cancer (mCRPC) who are iHRD+ and who have progressed on a second generation hormonal agent (e.g. abiraterone or enzalutamide).

Secondary Objectives:

1. Determine the percent of iHRD+ mCRPC patients achieving radiographic response per RECIST 1.1 criteria following treatment with olaparib.

2. Determine the radiographic progression free survival (PFS) in iHRD+ mCRPC patients treated with olaparib.

3. Determine the PSA PFS according to PCWG3 criteria in iHRD+ mCRPC patients treated with olaparib.

4. Determine the overall survival in iHRD+ mCRPC patients treated with olaparib.

5. Assess the incidence and severity of adverse events according to the National Cancer Institute- Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Exploratory Objectives:

Correlative work will be conducted to assess differences in clinical outcomes in those with vs. without iHRD positivity. This work will also allow us to further understand the biology underlying these differences. Serial blood samples and metastatic tissue will be obtained at baseline and upon progression. Examples of studies to be conducted may include, but are not limited to:

1. Evaluate for differences in radiographic/PSA response and PFS in patients who are iHRD+ compared to patients who are iHRD-.

2. Evaluate for differences in radiographic/PSA response and PFS by specific HR gene involvement.

3. Compare iHRD signature to other functional methods of predicting HRD including large scale state transition (LST) score and COSMIC signature 3/8 status, Telomeric allelic imbalance (TAI) score.

4. Optimize iHRD signature based on the results of this trial and develop a pipeline for calling iHRD from targeted exome panels.

5. Conduct transcript profiling studies on metastatic tissue.

Primary Endpoint:

Lowest on-treatment PSA, following at least 12 weeks of olaparib in men with mCRPC who are iHRD+

Secondary Endpoints:

The following endpoints will be assessed in men with iHRD+ mCRPC treated with olaparib:

1. Radiographic response rate per RECIST 1.1 criteria

2. Radiographic progression free survival (PFS)

3. PSA PFS according to PCWG3 criteria

4. Overall survival

5. Incidence and severity of adverse events according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Study Design

This will be a single arm, Phase II study designed to evaluate the clinical activity of olaparib in mCRPC patients with evidence of HRR deficiency as determined using iHRD signature analysis. Patients will initially be screened for eligibility on the basis of a loss of heterozygosity (LOH) score optimized for UW OncoPlex, a clinical grade targeted sequencing assay. Eligible LOH score positive subjects will then enroll and receive treatment with olaparib 300 mg by mouth twice daily. One treatment cycle will be defined as 28-days, and consist of continuous daily dosing of olaparib. All patients will then undergo germline and somatic whole exome sequencing (WES) to assess iHRD status. Only those found to be iHRD+ will be used for the purpose of assessing the primary endpoint (i.e. best PSA response). Those patients that are LOH score-positive/iHRD-negative will be allowed to continue on treatment, however, and will be used in assessment of exploratory objectives. All patients will continue on androgen deprivation therapy (ADT) (i.e. surgical or medical castration), and should have a two-week washout from their most recent mCRPC therapy and weaned from steroids prior to enrolment.

PSA will be measured on day 1 of every third cycle. Radiographic assessment with bone and CT scans will occur every 12 weeks. The primary endpoint will be lowest on-treatment PSA and primary objective is to determine the PSA50 rate. Patients will be permitted to continue until disease progression by radiographic (per RECIST 1.1), PSA (per PWCG3 criteria) or clinical criteria (e.g. increasing pain), whichever comes first. Prior to completing 3 cycles of treatment, patients should not discontinue treatment for PSA progression alone. Patients will come off study at time of clinical, radiographic, or PSA progression. Secondary objectives will include assessment of radiographic PFS, PSA PFS, overall survival, and adverse events.

1.2.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Subject must be $\geq$ 18 years of age at the time of signing the informed consent form.

3. Individuals who have documented histologically confirmed adenocarcinoma of the prostate.

4. Subject must have evidence of castration resistant prostate cancer as evidenced by PSA progression (per Prostate Cancer Working Group 3 [PCWG3] criteria) and a castrate serum testosterone level (i.e. $\leq$ 50 mg/dL)[1].

5. PSA must be at least 2 ng/mL and rising on two successive measurements at least two weeks apart.

6. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT scan, MRI, or PET and is suitable for repeated assessment.

7. Must have progressed on abiraterone and/or a second generation AR antagonist (i.e. enzalutamide, apalutamide, or darolutamide). If these were given in the hormone sensitive setting, patients must also have progressed on at least one prior approved therapy for CRPC.

8. Must have archival tissue available or be willing to undergo metastatic biopsy in order to perform next-generation DNA sequencing and undergo whole exome sequencing.

9. Patient must have a positive LOH score on prior UW OncoPlex testing

10. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

    - Hemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    - Platelet count ≥ 100 x 10^9/L
    - Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN
    - Patients must have creatinine clearance estimated of ≥51 mL/min using the Cockcroft-Gault equation or based on a 24 hour urine test :

      $$\text{Estimated creatinine clearance} = \frac{(140\text{-age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$$

11. Eastern Cooperative Oncology Group (ECOG) performance status ≤2

12. Patients must have an estimated life expectancy ≥ 16 weeks.

13. Male patients must use a condom during treatment and for 3 months after the last dose of olaparib 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 ([see appendix C for acceptable methods]) if they are of childbearing potential

Exclusion Criteria

1. As judged by the investigator, any evidence of serious and/or unstable pre-existing medical or psychiatric condition which in the investigator's opinion makes it undesirable for the patient to participate in the trial.

2. Other malignancy unless curatively treated with no evidence of disease for ≥5 years except: adequately treated non-melanoma skin cancer and non-muscle invasive bladder cancer.

3. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.

4. Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia.

5. Patients with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

6. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks 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.

7. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

8. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

9. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are not receiving active treatment or who have a detectable viral load.

10. Patients with known active hepatitis (i.e. Hepatitis B or C).

    - Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible.

    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

11. Any previous treatment with PARP inhibitor, including Olaparib.

12. Any previous treatment with platinum chemotherapy in the metastatic castration-resistant setting.

13. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment.

14. Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.

15. Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

16. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

17. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).

18. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.

19. Involvement in the planning and/or conduct of the study.

20. 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.

Statistical Methods

Based on the PROFOUND study, we estimate a response rate of 20% (H0) in patients with any HR mutations (e.g. BRCA2, ATM, CDK12, CHEK2, etc).[2] We will require a 50% (H1) response rate in iHRD positive patients to justify further development of this approach for selecting patients for olaparib treatment. Therefore, assuming we enroll 20 iHRD positive patients, this study would provide 87% power at a one-sided alpha of 0.03 to detect a 50% response rate compared to the null rate of 20%. Given that prior experience has shown that ~75% of patients with a positive LOH score will also have evidence of iHRD positivity, we will enroll a total of 30 patients to identify at least 22 iHRD positive subjects. This should allow for a drop out rate of 10% to ensure that at least 20 iHRD positive subjects are able to reach 12 weeks of treatment for the primary endpoint analysis.

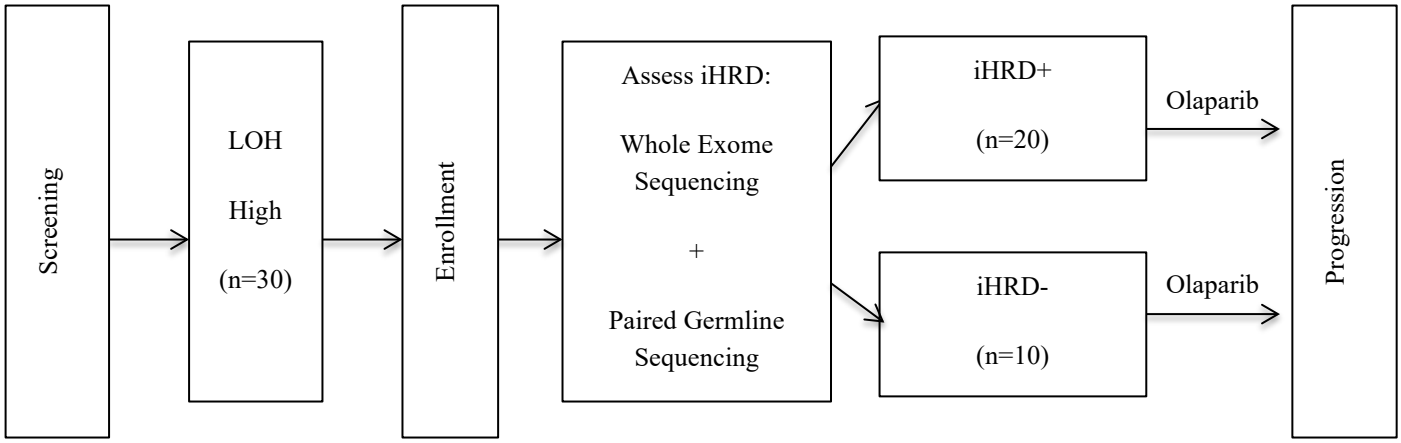
The primary objective is to determine the percentage of patients who are iHRD+ that achieve a PSA_{50} response (i.e. ≥50% decline in PSA from baseline). The lowest on treatment PSA will be defined as the lowest value following at least 12 weeks of treatment (i.e. the beginning of Cycle 4). The PSA50 response rate will be calculated along with 90% confidence intervals (CI). PSA changes will be presented as waterfall plots per PCWG3 recommendations. If a patient drops out

of the study prior to assessing best PSA response he will be considered as not having had a PSA50 response. However, an additional study subject will be enrolled to ensure an adequate number of subjects are available to estimate the PSA50 response rate.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study Design



LOH loss of heterozygosity; iHRD integrated homologous recombination deficiency

2. INTRODUCTION

2.1 Background and Study Rationale

METASTATIC CASTRATION RESISTANT PROSTATE CANCER:

Prostate cancer remains the second leading cause of cancer death among American men despite significant treatment advances in the past decade.[3] Advanced prostate cancer is an androgen-dependent malignancy, and the mainstay of treatment is androgen deprivation therapy and other hormonally targeted agents. However, resistance to these therapies inevitably develop, leading to the late and inevitably fatal disease state known as metastatic castration resistant prostate cancer (mCRPC). Resistance is thought to be conferred by various mechanisms, including increased intratumoral steroidogenesis, increased androgen receptor expression, and constitutively active androgen receptor splice variants. In addition there are several somatic genomic alterations that are associated with aggressive disease, including *TP53* mutations or deletions, *PTEN* loss, and defects in DNA-repair genes.[4] While recent approvals have expanded the treatment toolbox for patients with certain genetic alterations, the continued lethality of this disease highlights the need for additional therapeutic options.

HOMOLOGOUS RECOMBINATION DEFICIENCY AND RESPONSE TO PARP INHIBITORS:

Inactivating mutations in homologous recombination (HR) genes have been associated with improved responses to PARP inhibitors (PARPi) in men with mCRPC, likely through the induction of synthetic lethality. The TOPARP-A trial observed a response rate to the PARPi olaparib of 88% in men with homozygous deletions or deleterious mutations in DNA-repair genes compared to 6% in men without these alterations.[5] Further work has shown that response rates to PARP inhibitors vary dramatically depending on the affected gene.[6,7] 83.3% of men with *BRCA 1/2* alterations responded to olaparib (50% decline in PSA or RECIST 1.1 objective response) in the TOPARP-B trial compared to 10.5% with ATM mutations and 0% with *CDK12* mutations.[7] The finding of heterogeneous clinical outcomes based on affected gene has been recapitulated in both the TRITON2 and PROfound studies.[2,6] This variability in response underscores the problem with relying on 3-15 gene panels to define homologous recombination deficiency (HRD) for the purpose of selecting patients for treatment with PARPi. Furthermore, there is also a subset of patients without known deleterious mutations who still respond to treatment with a PARPi.[5] Taken together, these observations suggest that defects in DNA-repair genes are an imperfect biomarker to predict response to PARP inhibition and highlight the need for development of novel predictive strategies.

Differences in response to PARPi by affected gene may partially be explained by the fact that not all genes have the same biologic significance in terms of their role in mediating homologous recombination repair. In addition, next generation sequencing (NGS) assays looking for mutation defects in specific genes will miss epigenetic and cryptic events that result in HRD. Therefore, functional measures of HRD should provide a more reliable means for selecting patients who would benefit from treatment with a PARP inhibitor.

PREDICTING HOMOLOGOUS RECOMBINATION DEFICIENCY:

Homologous recombination repair (HRR) is a key pathway involved in resolving double-stranded DNA (dsDNA) breaks. HRR utilizes the undamaged sister chromatid as a template in order to produce error-free repair of the dsDNA damage.[8] When functional defects occur in this pathway by germline and/or somatic events, characteristic genome wide alterations occur, which result in predictable tumor signatures that can be called using bioinformatic tools. This HR deficiency signature calling has the potential to complement existing genomic biomarkers being developed to identify those likely to benefit from PARPi treatment.[9]

Several scores have been developed in an attempt to identify functional loss of HR activity, however, there are important limitations to the most widely used approaches[10-13]. An LOH-based score has been validated in epithelial ovarian cancer to strongly associate with functional defects in *BRCA1* and *BRCA2* as well as methylation of the promoter region of *RAD51C*, another gene in the HR pathway.[10] Although this score may capture an additional subset of patients who have HRD tumors than those captured by NGS alone, it is impacted by tumor ploidy and cellularity and thus may lack specificity. The COSMIC 3 signature has been developed based on unique genomic alterations associated with the loss of *BRCA1*/*BRCA2*.[14,15] However, this signature does not appear to reliably discriminate between responder/non-responders to olaparib (Figure 2).

To address these shortcomings, our group has developed an integrated approach to calling HRD signatures (iHRD - integrated Homologous Recombination Deficiency), with the goal of more reliably defining prostate cancer tumors that will be sensitive to DNA damaging therapeutics such as PARPi. This signature is a multiparametric classification that was defined using 418 patient samples from the Stand Up 2 Cancer (SU2C) repository and was subsequently validated on a set of cases from our UW rapid autopsy program. iHRD was more closely associated with improved clinical outcomes in patients receiving olaparib on the TOPARP-B study (Figure 2)[5]. Importantly, iHRD also allows us to identify *11-12% of mCRPC patients who do not have mutations in HR genes but who we would predict to have functional loss of HR and therefore stand to benefit from PARP inhibition* (Figure 3).

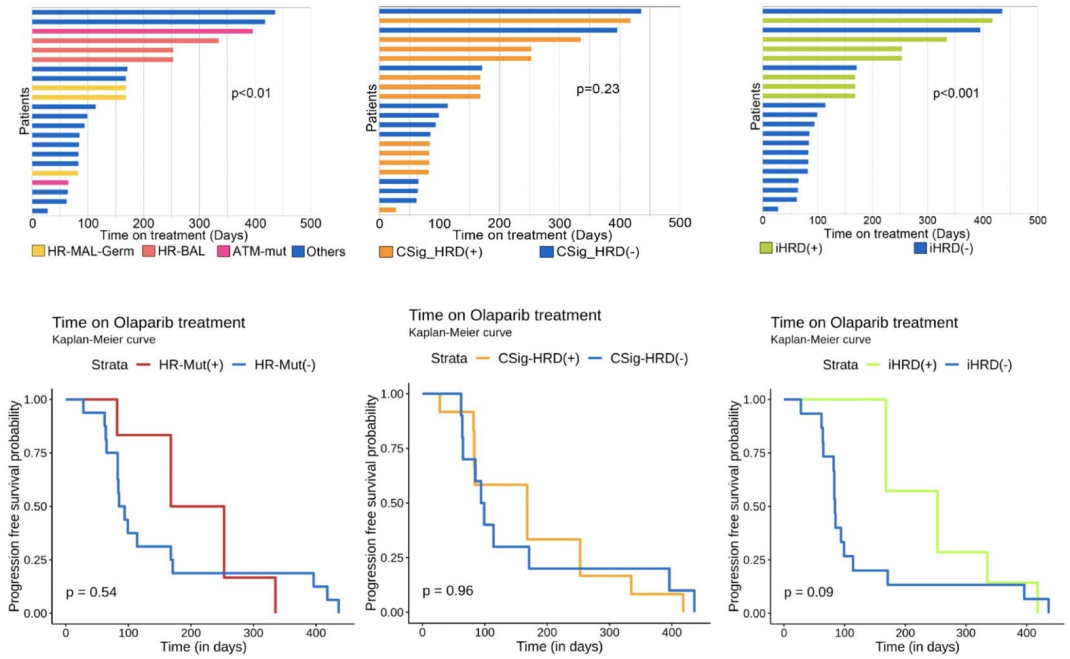


Figure 2. iHRD accurately predicts time on olaparib treatment. Data from 22 clinical cases of men with mutations in HRR genes treated with olaparib was re-analyzed, with time on olaparib treatment stratified by HRD mutational status, COSMIC3 signature and iHRD status. iHRD was more closely associated with time on olaparib than other approaches. iHRD correlated with time on olaparib treatment (top). Kaplan-Meier estimates showed a significant association between time on olaparib treatment and iHRD positivity; however, neither HR-biallelic loss nor COSMIC3 signature was associated with longer time on treatment.

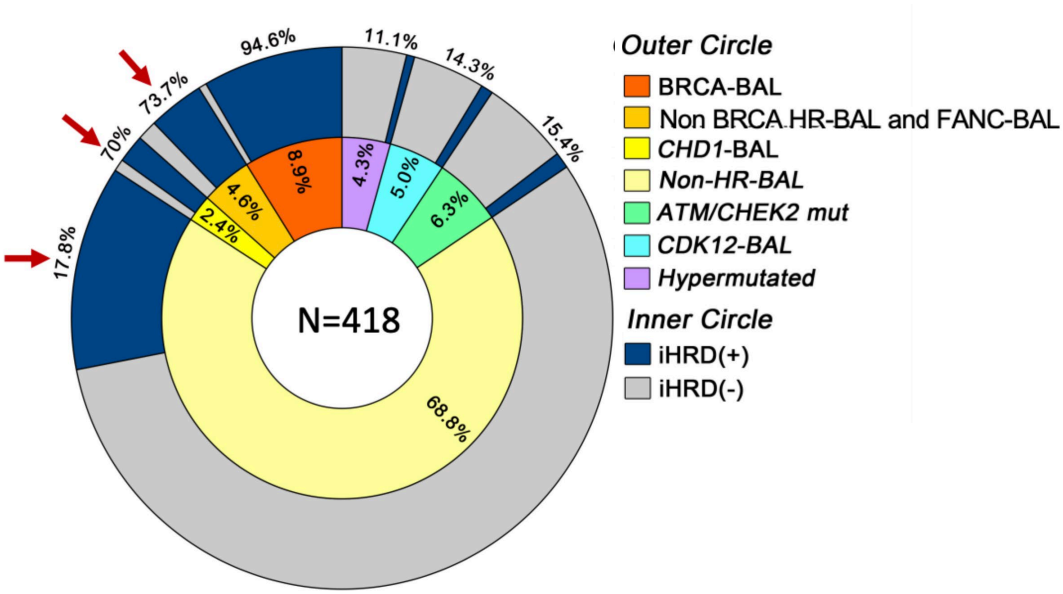


Figure 3. iHRD distribution across HR mutant subgroups. Spectrum of iHRD distribution across homologous recombination (HR) and putative HR associated gene mutant subgroups. Bi-allelic BRCA1, BRCA2, ATM, and PALB2 as biomarkers would potentially miss 65 of 107 iHRD+ mCRPC.

OLAPARIB BACKGROUND

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB).

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerization (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.

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as prostate cancers in patients with *BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Olaparib is currently FDA approved for men with metastatic castration resistant prostate cancer who have germline or somatic defects in any one of 14 HRR genes and who have progressed following treatment with enzalutamide or abiraterone. This approval was granted on the basis of the PROfound study – a Phase III randomized, open-label, multi-center trial[16]. Patients were eligible to enroll if they had mCRPC and had previously received either enzalutamide or

abiraterone and who had HRR gene alterations. Men received either olaparib 300mg twice daily or investigator's choice of either abiraterone or enzalutamide. The primary endpoint was progression free survival (PFS) in the group with *BRCA1*, *BRCA2* and/or *ATM* mutations (Cohort A). A second cohort consisted of patients with mutations in other HR repair-associated genes (Cohort B). Secondary endpoints were analyzed in a hierarchical fashion to control for trial-wide type 1 error associated with multiple testing, which occurred in the following order: objective response rate (Cohort A), PFS (combined Cohorts A and B), time to pain progression (Cohort A), and overall survival (Cohort A).

The primary endpoint of PROfound was met, with a PFS of 7.4 months vs. 3.6 months (P<0.001) in the olaparib vs. control groups for Cohort A. Secondary endpoints also favored the olaparib group, with an objective response rate in Cohort A of 33% vs. 2% in control group (P<0.001), median PFS of 5.8 months vs. 3.5 months for combined Cohorts A and B (P<0.001), median overall survival of 18.5 months vs. 15.1 months for Cohort A (P=0.02) and median overall survival of 17.5 months vs. 14.3 months for combined Cohorts A and B (P=0.0063). These results led the FDA to approve olaparib for a broad group of mCRPC patients with somatic or germline alterations in *BRCA1*, *BRCA2* or any of 12 additional HR repair pathway genes.

It should be noted that data supporting the use of olaparib in patients with non-*BRCA* mutations is sparse. There was no clear difference in PFS observed in either *ATM* (N=86) or *CDK12*-mutated (N=89) (Figure 2B and Supplemental Figure S5) patients enrolled on PROfound. In addition, the reported PSA and radiographic response rates for *ATM* (5.3% and 8.3%, respectively) and *CDK12*-mutated mCRPC (0% for both) was also low in TOPARP-B[7]. These results highlight the need for refinement of HRD biomarkers.

HYPOTHESIS:

Based on these observations, we *hypothesize that iHRD signature analysis will allow us to identify more men who are likely to benefit from PARP inhibitors, including those (11-12% of mCRPC population) who are otherwise excluded from clinical trials evaluating these agents.* We therefore plan to conduct a Phase II study to evaluate the utility of using iHRD signature analysis to select patients for treatment with olaparib.

2.2 Benefit/Risk Assessment

Olaparib is an FDA approved therapy for men with mCRPC and mutations in genes associated with homologous recombination repair based on improved progression free survival compared to novel hormonal agents (i.e. abiraterone or enzalutamide)[17]. This trial will include men with mCRPC and evidence of HRD based on a novel integrated genomic signature (iHRD). Based on the aforementioned rationale, we anticipate that olaparib will be effective in this patient population. One benefit of this study is access to a potentially efficacious antineoplastic medication that would not otherwise be available for a subset of men with mCRPC. Further, men in this study will have already progressed on at least one approved therapy for mCRPC, and effective treatment options remain somewhat limited for this patient population.

Risks of participating in this study are the known toxicities of olaparib, including hematologic toxicities, infections associated with myelosuppression, gastrointestinal toxicity, venous

thromboembolic events and risk of secondary leukemias/myelodysplastic syndrome[17]. For information on all identified and potential risks with olaparib refer to the current version of the IB. Overall, the investigators feel that the benefits of participating in this study outweigh the risks of participation.

3. OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVE:

Determine the percent of patients achieving a ≥50% reduction in PSA (PSA50 response) following at least 12 weeks of treatment with olaparib 300mg twice daily in men with metastatic castration-resistant prostate cancer (mCRPC) who are iHRD+ and who have progressed on a second generation hormonal agent (e.g. abiraterone or enzalutamide).

3.2 SECONDARY OBJECTIVES:

6. Determine the percent of iHRD+ mCRPC patients achieving radiographic response per RECIST 1.1 criteria following treatment with olaparib.

7. Determine the radiographic progression free survival (PFS) in iHRD+ mCRPC patients treated with olaparib.

8. Determine the PSA PFS according to PCWG3 criteria in iHRD+ mCRPC patients treated with olaparib.

9. Determine the overall survival in iHRD+ mCRPC patients treated with olaparib.

10. Assess the incidence and severity of adverse events according to the National Cancer Institute- Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

3.3 EXPLORATORY OBJECTIVES:

Correlative work will be conducted to assess differences in clinical outcomes in those with vs. without iHRD positivity. This work will also allow us to further understand the biology underlying these differences. Serial blood samples and metastatic tissue will be obtained at baseline and upon progression. Examples of studies to be conducted may include, but are not limited to:

1. Evaluate for differences in radiographic/PSA response and PFS in patients who are iHRD+ compared to patients who are iHRD-.

2. Evaluate for differences in radiographic/PSA response and PFS by specific HR gene involvement.

3. Compare iHRD signature to other functional methods of predicting HRD including large scale state transition (LST) score and COSMIC signature 3/8 status, Telomeric allelic imbalance (TAI) score, and presence of underlying HRR mutation.

4. Optimize iHRD signature based on the results of this trial and develop a pipeline for calling iHRD from targeted exome panels.

5. Conduct transcript profiling studies on metastatic tissue.

3.4 PRIMARY ENDPOINT:

Lowest on-treatment PSA, following at least 12 weeks of olaparib in men with mCRPC who are iHRD+

3.5 SECONDARY ENDPOINTS:

The following endpoints will be assessed in men with iHRD+ mCRPC treated with olaparib:

1. Radiographic response rate per RECIST 1.1 criteria
2. Radiographic progression free survival (PFS)
3. PSA PFS according to PCWG3 criteria
4. Overall survival
5. Incidence and severity of adverse events according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

4. STUDY DESIGN

4.1 Overall Design

This will be a single arm, Phase II study designed to evaluate the clinical activity of olaparib in mCRPC patients with evidence of HRR deficiency as determined using iHRD signature analysis. Patients will initially be screened for eligibility on the basis of a loss of heterozygosity (LOH) score optimized for UW OncoPlex, a clinical grade targeted sequencing assay. Eligible LOH score positive subjects will then enroll and receive treatment with olaparib 300 mg by mouth twice daily. One treatment cycle will be defined as 28-days, and consist of continuous daily dosing of olaparib. All patients will then undergo germline and somatic whole exome sequencing (WES) to assess iHRD status. Only those found to be iHRD+ will be used for the purpose of assessing the primary endpoint (i.e. best PSA response). Those patients that are LOH score-positive/iHRD-negative will be allowed to continue on treatment, however, and will be used in assessment of exploratory objectives. All patients will continue on androgen deprivation therapy (ADT) (i.e. surgical or medical castration) and should have a two-week washout from their most recent mCRPC therapy and weaned from steroids prior to enrolment.

PSA will be measured on day 1 of each treatment cycle. Radiographic assessment with bone and CT scans will occur every 12 weeks. The primary endpoint will be lowest on-treatment PSA and primary objective is to determine the PSA50 rate. Patients will be permitted to continue until disease progression by radiographic (per RECIST 1.1), PSA (per PWCG3 criteria) or clinical criteria (e.g. increasing pain), whichever comes first. Prior to completing 3 cycles of treatment, patients should not discontinue treatment for PSA progression alone. Patients will come off study at time of clinical, radiographic, or PSA progression. Secondary objectives will include assessment of radiographic PFS, PSA PFS, overall survival, and adverse events.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 5.5 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.2 Scientific rationale for study design

Overall rationale and study population:

The purpose of this study is to explore the efficacy of using a functional method of calling HRR deficiency (HRD) to predict response to olaparib. Men with mCRPC will be eligible if they have a positive LOH score on metastatic tissue and/or cell-free circulating tumor DNA (ctDNA), which has been associated with response to PARP inhbition[10]. They are eligible for inclusion into the study if they have progressed on abiraterone or enzalutamide, which is in concordance with the current population for which olaparib is indicated.

Study design:

This is a single arm, Phase II study designed to provide an initial estimate of clinical activity of olaparib in mCRPC patients that have iHRD+ tumors. Because there is no control group this study will not be blinded.

Primary and secondary outcome measures:

Lowest on-treatment PSA was chosen as a primary endpoint, as decline in PSA is generally associated with tumor control and can be assessed as early as 12 weeks. Radiographic response rate was not chosen as many prostate cancer patients have primarily osseous metastases and are not evaluable per RECIST criteria. This study follows the PCWG3 criteria for assessing PSA and defining PSA progression[1]. Secondary outcomes included are also reflective of PCWG3 guidelines.

4.3 Justification for dose

The dose of olaparib used in this study is 300 mg twice daily, which is the currently FDA approved dose.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study. Follow up will continue for up to one year after the last patient discontinues treatment.

5. STUDY POPULATION

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures, refer to section 5.4.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Subject must be $\geq$ 18 years of age at the time of signing the informed consent form.

3. Individuals who have documented histologically confirmed adenocarcinoma of the prostate.

4. Subject must have evidence of castration resistant prostate cancer as evidenced by PSA progression (per Prostate Cancer Working Group 3 [PCWG3] criteria) and a castrate serum testosterone level (i.e. $\leq$ 50 mg/dL)[1].

5. PSA must be at least 2 ng/mL and rising on two successive measurements at least two weeks apart.

6. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT scan, MRI, or PET and is suitable for repeated assessment.

7. Must have progressed on abiraterone and/or a second-generation AR antagonist (i.e. enzalutamide, apalutamide, or darolutamide). If these were given in the hormone sensitive setting, patients must also have progressed on at least one prior approved therapy for CRPC.

8. Must have archival tissue available or be willing to undergo metastatic biopsy in order to perform next-generation DNA sequencing and undergo whole exome sequencing.

9. Patient must have a positive LOH score on prior UW OncoPlex testing

10. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

- Hemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN
- Patients must have creatinine clearance estimated of ≥51 mL/min using the Cockcroft-Gault equation or based on a 24 hour urine test:

$$\text{Estimated creatinine clearance} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$$

11. Eastern Cooperative Oncology Group (ECOG) performance status ≤2

12. Patients must have an estimated life expectancy ≥ 16 weeks.

13. Male patients must use a condom during treatment and for 3 months after the last dose of olaparib 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 ([see appendix C for acceptable methods]) if they are of childbearing potential

5.2 Exclusion criteria

1. As judged by the investigator, any evidence of serious and/or unstable pre-existing medical or psychiatric condition which in the investigator's opinion makes it undesirable for the patient to participate in the trial.

2. Other malignancy unless curatively treated with no evidence of disease for ≥5 years except: adequately treated non-melanoma skin cancer and non-muscle invasive bladder cancer.

3. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.

4. Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia.

5. Patients with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

6. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks 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.

7. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

8. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

9. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are not receiving active treatment or have a detectable viral load.

10. Patients with known active hepatitis (i.e. Hepatitis B or C).

    – Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible.

    – Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

11. Any previous treatment with PARP inhibitor, including Olaparib.

12. Any previous treatment with platinum chemotherapy in the metastatic castration-resistant setting.

13. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment.

14. Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.

15. Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

16. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

17. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).

18. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.

19. Involvement in the planning and/or conduct of the study.

20. 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.

5.3 Lifestyle restrictions

No restrictions are required.

5.3.1 Meals and dietary restrictions

It is prohibited to consume grapefruit juice while on olaparib therapy.

5.3.2 Activity

Contraception

Male patients must use a condom during treatment and for 3 months after the last dose of olaparib 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 olaparib and for 3 months following the last dose of olaparib.

For details of acceptable methods of contraception refer to Appendix C Acceptable Birth Control Methods.

5.4 Screen failures

Screen failures are defined as patients who signed the informed consent form to participate in the clinical study but are not subsequently entered in the study. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

These patients should have the reason for study withdrawal recorded in the CRF.

5.5 Study Treatments

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to the drug olaparib.

Treatments administered

5.5.1 Investigational products

Table 2 Study Treatments

	Treatment 1
Study treatment name:	Olaparib
Dosage formulation:	Tablets
Route of administration	Oral
Dosing instructions:	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. Olaparib tablets can be taken with or without food.
Packaging and labelling	Study treatment will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures. Each container will be labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.

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.

5.6 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized site staff may dispense study treatment. Lynparza will be supplied from commercial stock, as bulk supplies to a single site only. The Sponsor will be responsible for labelling and onward distribution to sub-sites if applicable. At site, all study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

5.7 Treatment compliance

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer olaparib. They will receive a pill diary as shown in Appendix D. Study site staff will make tablet counts at regular intervals during treatment. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses.

Any change from the dosing schedule, does interruptions, dose reductions, dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager is responsible for managing the IMP from receipt by the study site until the destruction or return of all unused IMP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IMP.

5.8 Concomitant therapy

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over-the-counter or

prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Anti-emetics/Anti-diarrheals

From screening part 2 onwards, should a patient develop nausea, vomiting and/or diarrhea, then these symptoms should be reported as AEs (see section 8.3) and appropriate treatment of the event given.

Medications that may NOT be administered

Table 4 Prohibited medications

Prohibited medication/class of drug:	
Anticancer therapy: Chemotherapy Immunotherapy Radiotherapy (except palliative) Biological therapy Other novel agents	Not permitted while the patient is receiving study medication
Live virus vaccines Live bacterial vaccines	Not permitted while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

Table 5 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir	Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use.
Moderate CYP3A inhibitors: ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	• Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg twice daily for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards. • Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards. • After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.
Strong inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort	Strong or moderate CYP3A inducers should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib.
Moderate CYP3A inducers: bosentan, efavirenz and modafinil	If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of olaparib.

Table 5 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
• CYP3A4 substrates with narrow therapeutic margin: cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, and tacrolimus • CYP2B6 substrates: bupropion, efavirenz • OATP1B1substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate • BCRP substrates: methotrexate, rosuvastatin • P-gp substrates: simvastatin, pravastatin, dabigatran, digoxin and colchicine	Effect of olaparib on other drugs Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if statins or sensitive CYP3A4 substrates are co-administered. Appropriate clinical monitoring is recommended for patients receiving P-gp substrates or CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin and low molecular weight heparin may be given concomitantly with olaparib and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (e.g apixaban and rivaroxaban) if possible.

Table 5 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Administration of other anti-cancer agents	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

5.8.1 Background medication

All patients will be maintained on androgen deprivation therapy (ADT) if they have not had a prior orchiectomy for the duration of the study. Patients may also be receiving osteoclast inhibitors for prevention of skeletal related events and these will be permitted to continue.

5.8.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the CRF.

5.9 Dose modification

Dose Reductions

In case a dose reduction is necessary, the Study treatment will be administered as follows:

Table 6 Dose reductions for olaparib to manage adverse events

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily	250 mg twice daily	200 mg twice daily

Table 7 Dose reduction for olaparib if patient develops moderate renal impairment

Initial Dose	Moderate renal impairment (calculated creatinine clearance by Cockcroft -Gault equation or based on a 24 hour urine test between 31 and 50 ml/min): Dose reduction
300 mg twice daily	200 mg twice daily

Table 8 Dose reductions for olaparib if patient has to start taking a strong or moderate CYP3A inhibitor

Initial Dose	Strong CYP3A inhibitor	Moderate CYP3A inhibitor
300 mg twice daily	100 mg twice daily	150 mg twice daily

For guidance on dose reductions for management of AEs (including renal impairment) refer to section 6.5.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see section 6.5.

When dose reduction is necessary patients will take one 150 mg tablet and one 100 mg tablet twice daily or two x 100 mg tablet twice daily (see Section 8.4.6), or one 150 mg tablet twice daily or one 100 mg tablet twice daily (see Section 6.5).

5.10 Treatment after the end of the study

Not applicable - please see Section 4.1 for details of treatment after the study database has been closed. discontinuation of treatment and patient withdrawal

5.11 Discontinuation of study treatment

Patients may be discontinued from investigational product (IP) in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the Clinical Study Protocol
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
- Study drug held for >4 weeks due to an AE

5.11.1 Procedures for discontinuation of study treatment

The investigator should instruct the patient to contact the site before or at the time if Study treatment is stopped. A patient that decides to discontinue Study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of Study treatment should be documented in the CRF (electronic or paper). All Study treatment should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing Study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

Any patient discontinuing investigational product should be seen post discontinuation for the evaluations and sample collections outlined in the study schedule.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Section 5.12) All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported within 24 hours as described in Section 6.4.2) and followed to resolution as above. Patients should be seen within 30 days after discontinuing study medication to collect and / or complete AE information. For guidance on reporting adverse events after the 30 day follow up period see Section 6.4.2.1.

Discontinuation of Study treatment, for any reason, does not impact on the patient´s participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints

and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

5.12 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time that the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Treating physician and Sponsor Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to protocol.

In order to support key endpoints of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- Lost to Follow-up: site personnel should check hospital records, the patients' current physician, and a publicly available death registry to obtain a current survival status. (The applicable CRF modules will be updated).
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries where it is possible to do so under applicable local laws to obtain current survival status. (The applicable CRF modules will be updated).

5.13 Withdrawal from the study

Patients are free to withdraw from the study at any time without prejudice to further treatment. Patients who withdraw consent for further participation in the study will not receive any further olaparib or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Sponsor Investigator will follow up AEs outside of the clinical study.

Biospecimens obtained, as part of trial participation will be retained.

6. STUDY ASSESSMENTS AND PROCEDURES

Assessments will be performed according to the Schedule of Activities (SoA).

6.1 Assessment of HRD

6.1.1 LOH Score

During pre-screening patients will be assessed for loss of heterozygosity (LOH) by the application of an LOH score that has been optimized for use on UW OncoPlex, a clinical grade sequencing assay. LOH events are detected using the R package Sequenza[18], which uses data from tumor-normal sample pairs to probabilistically estimate tumor cellularity, ploidy, and allele-specific copy number abnormalities. Whole genome duplication or loss events, which arise from non-HRD associated mechanisms, are disqualified[19]. Using custom scripts, the LOH score is defined as the ratio of the genome affected by loss of heterozygosity events relative to the total number of sequenced nucleotides for which the tumor copy number state can be successfully inferred[19].

6.1.2 iHRD Status

All patients will have iHRD status assessed during the screening phase by undergoing paired germline and somatic whole exome sequencing. iHRD is a genomic classification framework that incorporates LOH score, COSMIC Signature 3, COSMIC Signature 8, tumor ploidy, tumor purity and mutation burden to determine the classification status. The classification outcome is read as binary 1 and 0, equated to iHRD+ and iHRD- respectively.

6.2 Efficacy assessments

6.2.1 Primary Objective

The primary objective is to determine the percentage of men achieving at least a 50% decline in PSA (PSA50 response) after twelve weeks of treatment with Olaparib 300mg by mouth twice daily. PSA will be collected from peripheral blood every cycle during the treatment phase. The lowest on treatment PSA will be defined as the lowest value following at least 12 weeks of treatment (i.e. the beginning of Cycle 4).

6.2.2 Secondary and Exploratory Objectives

ORR and Radiographic Progression Free Survival

Radiographic assessments which include computed tomography scan of the chest, abdomen, and pelvis as well as a nuclear medicine bone scan will be conducted every 12 weeks (every 3 cycles) after screening. Radiographic response and progression will be defined per RECIST 1.1 criteria. RECIST 1.1 is an accepted methodology by regulatory authorities and will be used to assess tumor response in patients with soft tissue disease. For patients with bony disease, progression will be defined per PCWG3 criteria[1].

Exploratory Objectives

Correlative blood work and tissue analysis will be performed per the planned time points in the SoA. Full details of collection, processing, shipping, and storage of samples will be included in the Lab Manual.

6.3 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

6.3.1 Clinical safety laboratory assessments

Blood samples for determination of clinical chemistry and hematology will be taken at the times indicated in the assessment schedules as clinically indicated (see the SoA). Clinical laboratory safety tests will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the treating physician and sponsor investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are presented in this section in Table 9.

Table 9 Laboratory safety variables

Hematology/Hemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Hemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Absolute neutrophil count	S/P-Alkaline phosphatase (ALP)
B-Absolute lymphocyte count	S/P-Aspartate transaminase (AST)
B-Platelet count	S/P-Alanine transaminase (ALT)
B-Mean cell volume (MCV)	S/P-Albumin
	S/P-Potassium
	S/P-Calcium, total
Urinalysis (dipstick)	S/P-Sodium
	S/P- Urea or Blood Urea Nitrogen (BUN)
U-Hb/Erythrocytes/Blood	S/p- Total Protein
U-Protein/Albumin	
U-Glucose	

NB. In case a patient shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix A 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

6.3.1.1 Coagulation

· activated partial thromboplastin time (APTT) will be performed at screening and if clinically indicated

· international normalized ratio [20] 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.

6.3.1.2 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities as defined in Section 6.5.5.1

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.

6.3.2 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoA). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat, and the respiratory, cardiovascular, GI, musculoskeletal, neurological, and dermatological systems. Height will be measured at screening only. Focused physical examinations are to be utilized by the treating physician on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in section 6.4.7.

6.3.3 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the SoA. Body weight is also recorded at each visit along with vital signs.

6.3.4 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

In case of clinically significant ECG abnormalities, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding

6.4 Data Monitoring and Collection of Adverse Events

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

Trial monitoring will be in accordance with the Fred Hutchinson Cancer Research Center (FHCRC)/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

Additionally, scheduled meetings will take place weekly and will include the Sponsor Investigator (Michael Schweizer, MD), research nurse, data manager, and, when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol. During these meetings the Sub-Investigators/ Sponsor Investigator will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objective.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see section 8.3.3.

6.4.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

6.4.2 Time period and frequency for collecting AE and SAE information

Adverse Events will be collected from time of enrolment throughout the treatment period and including the follow-up period until last contact.

SAEs will be recorded from the time of signing of informed consent form.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

6.4.2.1 Adverse events after the end of treatment visit

For Pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after end of treatment should be reported to AstraZeneca Patient Safety 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.

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 AstraZeneca, Patient Safety.

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. This includes new AEs/SAEs in patients still being followed up for survival but who have completed their end of treatment visit.

6.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs/non-serious AEs/AEs of special interest (as defined in Section 6.4.13, will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Any SAE or non-serious adverse event that is ongoing at the time of the end of treatment visit, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary

6.4.4 Adverse event data collection

'The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade and changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused subject's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication'

- Description of AE

6.4.5 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures . Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

6.4.6 Adverse events based on signs and symptoms

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

6.4.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

6.4.8 Hy's law

Cases where a patient shows elevations in liver biochemistry require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix A for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law

6.4.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.4.10 New Cancers

The development of a new primary cancer should be reported as an AE (see Section 6.4.13 Olaparib Adverse Events of Special Interest) and would in most cases meet seriousness criteria (with the exception of some non-melanoma skin cancers). New primary malignancies are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

Adverse Events (AEs) for malignant tumours 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. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is not the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

6.4.11 Lack of efficacy

When there is deterioration in the cancer, for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

6.4.12 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the CRF but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 8.4.1 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in theCRF.

Deaths with an unknown cause should always be reported as a SAE. A postmortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

6.4.13 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 Identified Risks of MDS/AML, and the Important Potential Risks of 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 characterise the event and gain a better understanding regarding the relationship between the event and study treatment.

6.5 Safety reporting and medical management

6.5.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

6.5.2 Pregnancy/Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 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) occurring from the date of the first dose until 3 months *after the last dose* should, if possible, be followed up and documented.

6.5.3 Overdose

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 CRF.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4.2. For other overdoses, reporting must occur within 30 days.

6.5.4 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening)or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 6.4.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

6.5.5 Management of adverse events

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed, and study treatment should be discontinued.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Section 6.5

6.5.5.1 Management of hematological toxicity

Management of anemia

Table 10 Management of anemia

Hemoglobin	Action to be taken
Hb < 10 *but* ≥ 8 g/dl (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dl. **Subsequent occurrences:** If Hb**< 10** *but* **≥ 9 g/dl** investigator judgement to continue olaparib with supportive treatment (eg. transfusion) *or* dose interrupt (for max of 4 weeks) and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step). If Hb**< 9** *but* **≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).

Hemoglobin	Action to be taken
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence), refer to guidance later in this section for the management of this.

Management of neutropenia, leukopenia and thrombocytopenia

Table 11 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to guidance later in this section for the management of this.

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in study treatment due to CTC 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. 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 CTC gr 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

6.5.5.2 Management of non-hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

Management of new or worsening pulmonary symptom

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If

significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

Management of nausea and vomiting

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 (ie 2 pieces of toast or a couple of biscuits).

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

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 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Primary Investigator.

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. After surgery study treatment can be restarted when the wound has healed. 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 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 12 Dose reductions for study treatment

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily	250 mg twice daily	200 mg twice daily

6.5.5.3 Renal impairment

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 dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24 hour urine test 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 twice daily.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that <<*select olaparib or study treatment*>> be discontinued.

6.6 Genetics

6.6.1 Collection of mandatory genetic samples

The patient's consent to participate in the genetic research components of the study is mandatory.

The tissue sample for genetic research will be obtained from the patients from archival tissue or from metastatic biopsy during pre-screening period and post-treatment.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Genetic signatures indicating homologous recombination deficiency will be analyzed. This analysis is required to include the patient in the study.

6.7 Biomarkers

Optional samples for biomarker research that should be collected from patients in the study where possible are the following:

- Tumor biopsies will be taken at baseline and at progression for investigation of genetic signatures and transcriptome analysis to evaluate their association with the observed clinical responses to olaparib.
- Please refer to the Laboratory Manual for further details regarding blood sample collection, shipping and storage.

In addition, blood will be collected, and analysis may be performed on exploratory biomarkers thought to play a role in homologous recombination deficiency including, but not limited to,

genome-wide analysis for RNA, serum analytes, or tissue biomarkers to evaluate their association with observed clinical responses to olaparib.

Other samples may be used for research to develop methods and further refine assays for predicting response to olaparib and clarifying mechanisms of resistance. All samples will be collected at the timepoints indicated in the SoA. Details regarding the collection, processing, shipping, and storage of samples for exploratory research will be defined in the Laboratory Manual.

6.7.1 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 5 years from the date of the Last Patient's Last Visit, after which they will be destroyed. Samples will be stored at the University of Washington and/or Fred Hutchinson Cancer Research Center (UW/FHCRC). These samples may also be sent to our research partners participating in this study, including Astra Zeneca. Specimens will not be used for reasons unrelated to this research study. All specimens will be kept in locked research laboratories at UW/FHCRC. The Sponsor Investigator will supervise the use of these specimens. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. Statistical Considerations

6.8 Sample size determination

Based on the PROFOUND study, we estimate a response rate of 20% (H0) in patients with any HR mutations (e.g. BRCA2, ATM, CDK12, CHEK2, etc).[2] We will require a 50% (H1) response rate in iHRD positive patients to justify further development of this approach for selecting patients for olaparib treatment. Therefore, assuming we enroll 20 iHRD positive patients, this study would provide 87% power at a one-sided alpha of 0.03 to detect a 50% response rate compared to the null rate of 20%. Given that prior experience has shown that ~75% of patients with a positive LOH score will also have evidence of iHRD positivity, we will enroll a total of 30 patients to identify at least 22 iHRD positive subjects. This should allow for a drop out rate of 10% to ensure that at least 20 iHRD positive subjects are able to reach 12 weeks of treatment for the primary endpoint analysis.

6.9 Statistical analyses

6.9.1 Efficacy analyses

Primary Objective

The primary objective is to determine the percentage of patients who are iHRD+ that achieve a PSA_{50} response (i.e. ≥50% decline in PSA from baseline). The lowest on treatment PSA will be defined as the lowest value following at least 12 weeks of treatment (i.e. the beginning of Cycle 4). The PSA50 response rate will be calculated along with 90% confidence intervals (CI) using Wilson's method. PSA changes will be presented as waterfall plots per PCWG3 recommendations. If a patient drops out of the study prior to assessing best PSA response he will be considered as not having had a PSA50 response.

ORR Response

For patients with measurable disease, ORR will be defined as a 30% decrease from baseline per RECIST 1.1 criteria at any time point. The percent of patients with ORR and 90% CI, calculated using Wilson's method, will be provided. Radiographic responses will be presented as waterfall plots.

rPFS, PSA PFS, OS

These endpoints are defined in section 3.5. The distributions of each endpoint will be estimated using the Kaplan-Meier method. Median times to event will be reported with 90% CIs using linear interpolation between steps of the survival curve.

Exploratory Objectives

Response rates and time to event endpoints as described above will be compared between patients who are iHRD+ and iHRD-. PSA and radiographic response rates including percentage and 90% CIs, calculated using Wilson's method, will be reported. Differences in response rates will be quantified using logistic regression with no additional adjustment. Time to event endpoints will be compared with log-rank tests.

If dropout is greater than anticipated, primary and secondary endpoint analyses will still be based on patients with 12 weeks of follow-up. However, the exploratory analysis will examine extreme scenarios in which endpoints for dropouts are imputed to minimize differences between iHRD+ and iHRD- patients.

We will additionally be looking at association between response rate and different predictors of homologous recombination deficiency including large scale state-transition (LST) score, COSMIC signature 3/8, and presence of underlying HR mutation. We will report the presence of underlying HR mutations in both the iHRD(+) and iHRD(-) groups. Depending on the final makeup of the study population, we will report PSA and radiographic response rates among various subsets which may include iHRD(+) and *BRCA* mutant iHRD(-) patients. We will also use the results of this trial to optimize iHRD classification framework and develop a clinical pipeline for calling iHRD from targeted exome panels. We will also describe the results of transcript profiling studies from tumor biopsies and compare pre and post treatment profiles.

6.9.2 Safety analyses

All patients who initiate study treatment will be evaluated for safety, combined across both cohorts. Adverse events will be summarized as number (%) of patients by system organ class, CTCA term and grade, where grade is the maximum across a patient's treatment period.

7. REFERENCES

1. Scher HI, Morris MJ, Stadler WM, 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):1402-1418.
2. Hussain M. Profound: Phase 3 Study of Olaparib Versus Enzalutamide or Abiraterone For Metastatic Castration-Resistant Prostate Cancer (mCRPC) With Homologous Recombination Repair (HRR) Gene Alterations. Paper presented at: ESMO Congress 20192019.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.
4. Sartor O, de Bono JS. Metastatic Prostate Cancer. *N Engl J Med.* 2018;378(7):645-657.
5. Mateo J, Carreira S, Sandhu S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *The New England journal of medicine.* 2015;373(18):1697-1708.
6. Abida W, Campbell D, Patnaik A, et al. Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: analysis from the phase 2 TRITON2 study. *Clin Cancer Res.* 2020.
7. Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol.* 2020;21(1):162-174.
8. Ceccaldi R, Rondinelli B, D'Andrea AD. Repair Pathway Choices and Consequences at the Double-Strand Break. *Trends Cell Biol.* 2016;26(1):52-64.
9. Lord CJ, Ashworth A. BRCAness revisited. *Nature reviews Cancer.* 2016;16(2):110-120.
10. Abkevich V, Timms KM, Hennessy BT, et al. Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. *British journal of cancer.* 2012;107(10):1776-1782.
11. Birkbak NJ, Wang ZC, Kim JY, et al. Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents. *Cancer discovery.* 2012;2(4):366-375.
12. Popova T, Manie E, Rieunier G, et al. Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation. *Cancer Res.* 2012;72(21):5454-5462.
13. Polak P, Kim J, Braunstein LZ, et al. A mutational signature reveals alterations underlying deficient homologous recombination repair in breast cancer. *Nature genetics.* 2017;49(10):1476-1486.
14. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. *Nature.* 2013;500(7463):415-421.
15. Nik-Zainal S, Davies H, Staaf J, et al. Landscape of somatic mutations in 560 breast cancer whole-genome sequences. *Nature.* 2016;534(7605):47-54.
16. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med.* 2020.
17. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med.* 2020;382(22):2091-2102.

18. Favero F, Joshi T, Marquard AM, et al. Sequenza: allele-specific copy number and mutation profiles from tumor sequencing data. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2015;26(1):64-70.
19. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2017;18(1):75-87.
20. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213-223.

Appendix A Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

A 1 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.

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 AstraZeneca 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 (IP).

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.

A 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN 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 ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, 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 (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

A 3 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 ≥ 3 × ULN

- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

When the identification criteria are met the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Appendix A 2 for definition) by reviewing laboratory reports from all previous visits
- 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 Appendix A 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

A 4 Follow-up

A 4.1 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.

A 4.2 Potential Hy's Law criteria met

If the patient does meet PHL criteria 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 medically indicated.
- If at any time the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

A 5 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.

If there is an 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 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')

  – 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:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

A 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

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, then follow the subsequent process described in Appendix B 5.

- 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.

A 7 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 (eg, chronic or progressing malignant disease, severe infection or liver disease), or did the subject meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Appendix A 6*?*

If **No**: Follow the process described in Appendix A 4.1.

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 Appendix A 4.

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.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 6 Intensity rating scale:

The grading scales found in the revised National Cancer Institute CTCAE latest version (5.0) will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

For each episode of an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTC grade should be reported.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Acceptable Birth Control Methods

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

Male patients must use a condom during treatment and for 3 months after the last dose of olaparib 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). Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

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 trial and for at least 1 month after the last dose of study drug <<for 3 months after last dose *for male patients*>>. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception]
- Vasectomized sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD 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 (eg., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin / EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (eg., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom

Appendix D Pill Diary Template

Participant ID: Cycle Number:						
Day	Date	Number of Olaparib Capsules	Time of Dose	Number of Olaparib Capsules	Time of Dose	Notes
1			:AM		:PM	
2			:AM		:PM	
3			:AM		:PM	
4			:AM		:PM	
5			:AM		:PM	
6			:AM		:PM	
7			:AM		:PM	
8			:AM		:PM	
9			:AM		:PM	
10			:AM		:PM	
11			:AM		:PM	
12			:AM		:PM	
13			:AM		:PM	
14			:AM		:PM	
15			:AM		:PM	
16			:AM		:PM	
17			:AM		:PM	
18			:AM		:PM	

19			:AM		:PM	
20			:AM		:PM	
21			:AM		:PM	
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23			:AM		:PM	
24			:AM		:PM	
25			:AM		:PM	
26			:AM		:PM	
27			:AM		:PM	
28			:AM		:PM	

Appendix E Recommendations from Prostate Cancer Clinical Trials Working Group 3 (PCWG3)[1]

Suggested outcome measures for clinical trials in metastatic prostate cancer as excerpted from PCWG3 recommendations.[1]

E 1 PSA Progression

PSA progression is defined as the time from start of therapy to first PSA increase that is $\geq$ 25% and $\geq$ 2 ng/mL above the nadir, which is confirmed by a second values $\geq$ 3 weeks later (i.e., a confirmed rising trend).

E 2 Bone Progression

Progression in the bone is defined as at least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule). If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented. For all scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan. Date of progression is the date of the scan that first documents the second lesion. Changes in intensity of uptake alone do not constitute either progression or regression.