Phase II Study of Olaparib in Men with High-Risk Biochemically-Recurrent Prostate Cancer Following Radical Prostatectomy, with Integrated Biomarker Analysis

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INVESTIGATOR'S APPROVAL OF PROTOCOL

Title: **Phase II Study of Olaparib in Men with High-Risk Biochemically Recurrent Prostate Cancer, with Integrated Biomarker Analysis**

Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

SYNOPSIS

Title of Study: Phase II Study of Olaparib in Men with High-Risk Biochemically-Recurrent Prostate Cancer Following Radical Prostatectomy, with Integrated Biomarker Analysis

Investigators: Principle Investigator: -Catherine Handy Marshall, M.D.; Co-Investigator/ Protocol Author: Benjamin A. Teply, M.D.; Lead Pathologist: Tamara Lotan, M.D.; Statisticians: Hao Wang, Ph.D.; Brandon Luber, Sc.M.

Study Centers: Johns Hopkins, Baltimore, MD (lead); Thomas Jefferson, Philadelphia, PA, University of Nebraska, Omaha, NE

Concept and Rationale:

Disease Background: For men who previously received definitive treatment for prostate cancer and subsequently develop detectable prostate specific antigen (PSA), the clinical state is known as biochemically recurrent prostate cancer. The natural history for these patients is variable, and the risk for development of metastasis depends on the PSA Doubling Time (PSADT). For patients with PSADT < 6 months, the median metastasis-free survival is ~2 years in the absence of androgen deprivation therapy (ADT). The current standard of care treatment for patients with high risk biochemically recurrent prostate cancer is either surveillance or ADT. ADT has not been shown to provide a survival benefit in this setting, and the decision to initiate ADT will depend on patient preference and perceived risks of the disease. A non-hormonal therapy such as olaparib would provide an alternative to ADT as a potential treatment option for these patients.

Investigational Agent: Olaparib is a poly-ADP ribose polymerase (PARP) inhibitor that is FDA-approved for the treatment of advanced, refractory ovarian cancer. PARP functions in the DNA repair pathway, specifically by serving in base excision repair of DNA single strand breaks. Inhibition of PARP results in inability for cells to repair single strand breaks. Cells normally would employ the error-free homologous recombination pathway to repair such defects. However, in tumors that harbor defects in these DNA repair genes (such as BRCA1/2 or ATM), the strand breaks lead to chromosomal instability and eventually cell death. Olaparib also traps the PARP protein on DNA, leading to further cytotoxicity. A dose of 300mg (tablets) PO BID, which is bioequivalent to the FDA-approved dose of 400mg (capsules) PO BID, will be employed in this study.

Rationale for olaparib in high risk biochemically recurrent prostate cancer: Olaparib has demonstrated preliminary efficacy in metastatic castration-resistant prostate cancer. In a trial of 49 evaluable patients treated with olaparib, 11 / 49 experienced a PSA_{50} response, and every patient with a radiographic response also had a PSA_{50} response. Ten of 11 responders had mutations in DNA repair genes. While PARP inhibition is showing promise in these initial studies, reserving its use for end-stage patients may not be the optimal timing for olaparib therapy in some patients. In addition, PARP enzymes function in roles beyond DNA repair, and specifically for prostate cancer are involved transcriptional regulation of the androgen receptor. PARP inhibition has not been tested in earlier disease states for prostate cancer.

Several studies have recently been published describing the prevalence of DNA repair defects in prostate cancer. Based upon these large genomic analyses for cohorts of patients with prostate

cancer, we can estimate a range of likely prevalence for DNA repair defective tumors for patients with biochemically recurrent prostate cancer. For mutations detectable in tumor tissue, the prevalence for biochemically recurrent prostate cancer is likely between the 19-23%. The anticipated range for germline mutations is 5-12%. Therefore, the defects that likely predict sensitivity to olaparib are likely present in some of these patients. Yet, despite some encouraging preliminary data on a potential mutation signature that is predictive of response to olaparib, the optimal biomarker profile for response is probably not known at this time.

Rationale for correlative studies

Tumors will be sequenced for somatic genetic mutations in DNA repair genes (Foundation Medicine). The genes analyzed will include those commonly mutated (BRCA2, ATM, BRCA1, CHEK2, CDK12, RAD51, PALB2, FANCL). By cataloging the mutations present in the primary tumors for subjects in the study, correlative analysis associating response with specific mutations can be performed.

An alternative biomarker for tumor sensitivity to olaparib is through gene expression changes that may not be identified through genetic mutation analysis alone. Subjects will have tissue tested for RNA expression arrays for associating response to olaparib. For this assay, samples will be tested using the Decipher GRID microarray platform (GenomeDx). The gene expression profile will be inclusive of a metastasis signature and olaparib-sensitivity signature. A post-hoc analysis will be performed to evaluate these signatures, and further determine a gene expression profile that predicts response to olaparib.

An exploratory biomarker, beyond the DNA mutations and RNA expression changes, is a functional examination of PARP activity in the tumor. A protein-level assessment of PARP-1 and γH2AX through immunohistochemistry will be performed on prostatectomy tumor tissue. PARP-1 is the primary target of olaparib, and γH2AX is a protein present at sites of double strand DNA breaks. The expression of these markers will be qualitatively scored and levels of expression correlated with response to olaparib.

Primary Objective: To estimate the PSA response rate to olaparib in patients with high-risk biochemically recurrent prostate cancer while on treatment with olaparib, defined as a decline in PSA to 50% of baseline level, confirmed with a second measurement at least 4 weeks apart.

Secondary Objectives:

- To determine the safety/tolerability of olaparib in the biochemically-recurrent prostate cancer patient population.
- To estimate the median PSA progression-free survival.
- To estimate the median time to PSA doubling from baseline.
- To estimate the rate of durable undetectable PSA in patients responding to olaparib.

Exploratory Objectives:

- To estimate PSA_{50} response in "biomarker positive" patients, based upon tissue-based FoundationOne mutations in the pre-specified gene list (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or other DNA repair genes), if an enriched cohort is not accrued.
- To estimate PSA_{50} response in "biomarker negative" patients, based upon tissue-based mutations in the pre-specified gene list, if an enriched cohort is not accrued.

- To estimate PSA_{50} response rate for patients with and without a mutation on the pre-specified list, based upon plasma cell-free DNA analysis using the pre-specified gene list (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or other DNA repair genes).
- To develop a genetic mutation signature associated with response to olaparib. For this objective, the biomarker signature will not be defined *a priori* but instead this will involve an exploratory analysis.
- To develop an RNA expression signature associated with response to olaparib.
- To investigate any association between PARP-1 and γH2AX protein levels in tumor with response to olaparib.
- To estimate median metastasis-free survival.
- To estimate median time to next anti-cancer therapy.

Primary Endpoint: PSA_{50} response, defined as a decline in PSA to 50% of baseline level, confirmed with a second measurement at least 4 weeks apart.

Secondary Endpoints:

- Safety/Tolerability, defined as incidence of CTC v4.0 grade ≥3 toxicities experienced by patients on the trial.
- PSA progression-free survival, defined as a time from initiation on olaparib therapy until PSA increase of 25%, confirmed with another measurement at least 4 weeks later.
- Time to PSA doubling from baseline, defined as time from initiation of olaparib therapy until the PSA has increased to 200% of baseline value, confirmed with another measurement at least 4 weeks later.
- Undetectable PSA, defined as PSA < 0.1, lasting at least 12 weeks.

Exploratory Endpoints:

- *(If an enriched population is not accrued)* PSA_{50} response, defined as a decline in PSA to 50% of baseline level, confirmed with a second measurement at least 4 weeks apart, in "biomarker positive" patients based upon tissue-based testing for the pre-specified gene list (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or other DNA repair genes).
- *(If an enriched population is not accrued)* PSA_{50} response, defined as a decline in PSA to 50% of baseline level, confirmed with a second measurement at least 4 weeks apart, in "biomarker negative" patients, based upon based upon tissue-based testing for the pre-specified gene list.
- PSA50 response, defined as decline in PSA to 50% of baseline level, confirmed with a second measurement at least 4 weeks apart, in "biomarker positive" and "biomarker negative" patients, based upon plasma cell-free DNA analysis and the pre-specified gene list.
- To develop a DNA mutation signature for response based upon prostatectomy sample testing.
- To associate RNA expression array signature with response.
- To associate response to olaparib with baseline PARP-1 and γH2AX protein levels in prostatectomy specimens.

- Metastasis-free survival, defined as time from biochemical recurrence to radiographic development of metastatic disease.
- Time to next anti-cancer therapy, defined as time from biochemical recurrence to date of administration of prostate cancer therapy (such as ADT, oral antiandrogen, or other clinical trial agent).

Study Design: The proposed study is an open-label single-arm phase II trial. Eligible patients are those with non-metastatic biochemically-recurrent prostate cancer and a PSADT of ≤6 months and a minimum PSA of 1.0. After enrollment, patients will be treated with olaparib at the established dose of 300mg tablets by mouth twice daily. Patients will be followed monthly with clinic visits, safety labs (including CBC w/diff, Comp), PSA, and toxicity assessments. Treatment [with a minimum drug exposure of 12 weeks] will be continued until PSA doubling from study entry (confirmed with another measurement at least 4 weeks later), development of radiographic metastatic disease, or toxicity requiring drug cessation. CT scans and NM bone scans will be performed every 6 months for patients remaining on olaparib treatment.

After enrollment, patients will have tissue from their primary prostatectomy specimens sequenced for genomic DNA changes potentially predictive of olaparib response using the Foundation Medicine sequencing platform. In addition, tissue will be analyzed with RNA expression arrays using the Decipher GRID microarray platform (GenomeDx). The gene expression profile will be inclusive of a metastasis signature and olaparib-sensitivity signature. Tissue will also be analyzed for protein levels of PARP-1 and γH2AX at baseline. Plasma will be collected for cell-free DNA analysis.

This study will enroll up to 50 subjects. The study design will employ a stepwise adaptive statistical plan, derived in part from Biankin *et al*, *Nature* 2015 Oct 15;526(7573):361-70. The design is adapted from a multi-stage design, with interim stopping rules to determine futility or need for enrichment of the study population.

The study will initiate with a two-stage design in an unselected population. The assumptions for the trial of the unselected population are: null hypothesis of 0.1 PSA response rate and alternative hypothesis of 0.3 for the unselected population. The first stage is 20 subjects. If ≤2 subjects responds in the first stage, then unselected population study is halted for futility and an assessment of DNA mutations present in the initial cohort will be undertaken. If less than 3 subjects with a known/suspected deleterious mutation in the following genes (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or other DNA repair genes) have been accrued in the first stage, then the trial will proceed with enrichment. If 3 or more subjects with known/suspected deleterious mutation in the genes of interest have been accrued, then the trial will proceed with enrichment, as long as the response rate in that subset of subjects is ≥20%. In the case that 3 or more subjects have been accrued, yet the response rate in that subset is <20%, then the trial is halted for futility.

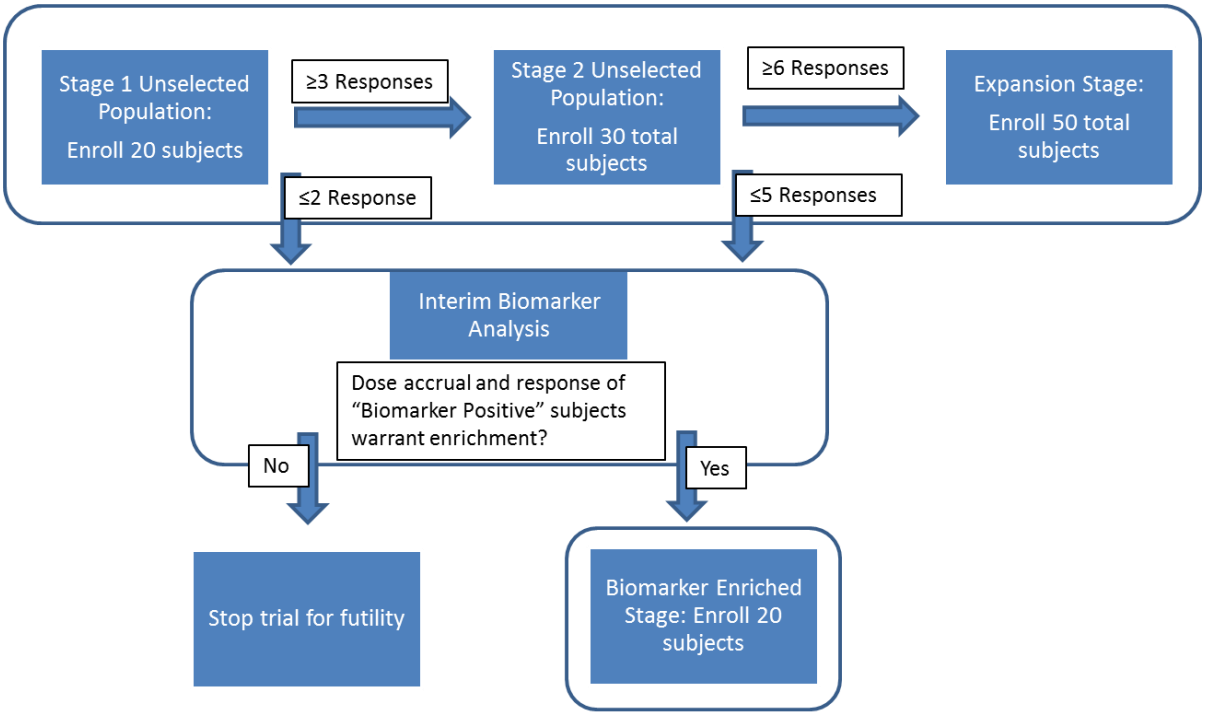
However, if ≥3 subjects among the first 20 respond, then additional 10 unselected subjects are accrued. If ≥6 subjects respond out of 30 in the unselected population after the second stage, then the null hypothesis is rejected in the unselected population and broad efficacy will be concluded. The trial proceeds to complete accrual of 50 subjects in order to better estimate PSA response rate and strengthen data for correlative studies. If <6 respond, then the null hypothesis is not rejected. Again, if less than 3 subjects with a known/suspected deleterious

mutation in the following genes (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or other DNA repair genes) have been accrued in the first and second stage combined, then the trial will proceed with enrichment. If 3 or more subjects with those mutations have been accrued, then enrichment will again proceed as long as the response rate in that subject of subjects is ≥20%.

An enriched population will be required to have a known/suspected deleterious mutation in of the genes listed above. The data for the enriched population will be analyzed separately from the data in the first (and second, if applicable) stage(s). The assumptions for the enriched population: null hypothesis of 0.3 PSA response rate, and alternative hypothesis of 0.6 for the biomarker selected population. The sample size for the selected population is 20 subjects. If ≥10 respond, the null is rejected for the biomarker selected population and efficacy will be concluded for the biomarker subgroup.

This design will have power for detecting an effect in the unselected population of 0.90-0.91 and a power for detecting an effect in the selected population (if there is no effect in the unselected) of 0.79-0.80, with an overall type I error 0.1-0.11, assuming the biomarker prevalence 10-15%, based upon 10,000 simulations of possible outcomes.

Schema:



Number of Patients: 50.

Our institution has a record of accruing 1-2 patients per month to trials in patients with biochemically recurrent prostate cancer with similar inclusion criteria. With opening at multiple sites, trial would be expected to fully accrue in 24 months or less. The primary endpoint is expected to be reportable within 30 months, or sooner, after trial activation.

Main Eligibility Criteria:

Inclusion:

1. Histologic diagnosis of adenocarcinoma of the prostate.
2. Prior local therapy with prostatectomy required, with available tissue from prostatectomy specimen to send for genomic and transcriptomic testing.
3. Prior salvage or adjuvant radiation therapy is allowed but not mandated. Radiation therapy must have been completed for at least 6 months.
4. Absolute PSA ≥1 ng/ml. Prior undetectable PSA post-prostatectomy is not required.
5. PSADT ≤6 months, based upon ≥3 consecutive measurements collected in the past 12 months, at least 4 weeks apart, calculated using MSKCC calculator
6. No radiographic evidence of metastatic disease by CT scan and bone scan, performed within the prior 4 weeks.
7. Serum testosterone ≥ 150 ng/dl.
8. Participants 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 ≥ 75 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
     Note: Patients with elevations in bilirubin, AST, or ALT should be thoroughly evaluated for the etiology of this abnormality prior to entry and patients with evidence of viral infection should be excluded.
   - Patients must have creatinine clearance estimated using the Cockcroft-Gault equation of ≥51 mL/min:

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

9. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix A).
10. Male participants and their partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination [see appendix E for acceptable methods], throughout the period of taking study treatment and for 3 months after last dose of study drug to prevent pregnancy in a partner.
11. *For enrichment stage of trial only (if necessary)*: Confirmation of a suspected/known deleterious mutation in a gene of interest (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or other DNA repair genes) via CLIA certified testing.

Exclusion:

1. Prior ADT in the past 6 months. Prior ADT in context of neoadjuvant/adjuvant primary; prior ADT for biochemical recurrence is allowed, as long as no ADT has been administered in past 6 months and testosterone has recovered (>150 ng/dl). The total duration of prior ADT should not exceed 24 months.

2. Prior oral anti-androgen (e.g. bicalutamide, nilutamide, enzalutamide, apalutamide), or androgen synthesis inhibitor (e.g. abiraterone, orteronel) in the past 6 months. 5-alpha reductase inhibitor therapy (e.g. finasteride, dutasteride) is allowed, as long as subject has been stable on medication for past 6 months.
3. Prior treatment with intravenous chemotherapy for prostate cancer.
4. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
5. Participation in another clinical study with an investigational product during the last 1 month.
6. Any previous treatment with PARP inhibitor, including olaparib.
7. Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome
8. 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.
9. Concomitant use of known strong CYP3A inducers (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 phenobarbital and 3 weeks for other agents.
10. Myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML.
11. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
12. 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, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.
13. Unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
14. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV).
15. Known hypersensitivity to olaparib or any of the excipients of the product.
16. Known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids
17. Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no.10)

Intervention and Mode of Delivery: Olaparib 300mg tablets by mouth twice daily.

Duration of Intervention and Evaluation: Patients will be treated until toxicity requiring cessation, doubling of PSA from baseline, confirmed by a second measurement at least 4 weeks apart, or clinical/radiographic progression, defined as development of symptoms related to prostate cancer or metastatic disease on CT or NM Bone Scan. Patients will be monitored monthly while on therapy. After completion of study treatments, they will be monitored for at least 1 month after any grade 2 or higher toxicities return to grade 1 or resolve.

Statistical Methods:

(a) Definition of primary endpoint: The primary endpoint of this study is PSA_{50} response, defined as a decrease in the PSA to 50% less than the baseline PSA upon enrollment in the trial. The decrease must be confirmed by a second measurement at least 4 weeks apart. For purposes of meeting the primary endpoint, patients will be considered to have done so if they have a PSA_{50} response only while on therapy with olaparib. PSA values will be measured monthly during the trial. All patients who are administered at least one dose of olaparib will be considered evaluable for the primary endpoint. If patients do not have follow-up PSAs after initiation olaparib therapy due to stopping therapy for toxicity or withdrawing consent, then they will be considered non-responders. If the biomarker-enriched stage is necessary, that cohort will be evaluated separately from the initial stage(s) of the trial.

(b) Definition of secondary endpoints:

i. Safety: Patients will be assessed for toxicities at each clinical evaluation. Toxicities will graded according to CTC v4.0 standardized grading scales. The incidence of grade 3-5 toxicities will be reported. Patients will be assessed for toxicity as long as they are taking olaparib, for at least 30 days after stopping, and will continue to be followed if olaparib is discontinued for toxicity until the toxicities improve to grade 1 or resolve.

ii. PSA progression-free survival (PFS): patients in this trial can remain on olaparib as long as they are not experiencing toxicity requiring cessation of drug, not experiencing clinical progression of disease, and until their PSA reaches a value that is double that of the value on enrollment in the study. However, for purposes of reporting this secondary endpoint, a standard definition of PSA progression per PCWG3 will be used. PSA PFS will be defined as an increase in 25% over a nadir value, confirmed by a follow-up PSA at least 4 weeks apart. The date of PSA progression will be the first value recorded (not the confirmatory value). If patients are removed from study prior to PSA progression, then they will be censored at that time.

iii. Time to PSA doubling from baseline: this endpoint is a time-to-event defined as time from initiation of olaparib therapy until the PSA has increased to 200% of baseline value, confirmed with another measurement at least 4 weeks later. The date of PSA doubling will be the first value recorded (not the confirmatory value).

iv. Undetectable PSA: A durable undetectable PSA endpoint will be defined as a patient on study with olaparib who achieves a PSA < 0.1, lasting at least 12 weeks. This endpoint will represent a durable complete biochemical response to olaparib. This endpoint can only be achieved while on therapy with olaparib, although the confirmatory values after initially achieving undetectable PSA may be measured while off therapy for olaparib.

(c) Analytic plan for primary objective: We will estimate the PSA_{50} response rate for the unselected population of patients. If a biomarker-selected population is accrued, it will be analyzed separately from the previously accrued unselected population. If a

biomarker-selected population is not accrued, analysis of response rates for "biomarker-positive" and "biomarker-negative" subjects, based upon the pre-specified gene list, will be reported as exploratory objectives.

(d) Analytic plan for secondary objectives:

i. Toxicity: these will be reported as a tabulated table by type and grade
ii. PSA PFS: We will use the Kaplan-Meier method to estimate the median PSA PFS.
iii. Time to PSA doubling from baseline: We will use the Kaplan-Meier method to estimate the median time to PSA doubling.
iv. Undetectable PSA: the durable complete PSA response rate will be estimated as number of patients achieving a durable complete PSA response divided by enrolled patients with a 95% confidence interval.

(e) Analytic plan for exploratory objectives:

i. *(if a biomarker-selected population is not accrued)* Biomarker positive and biomarker negative PSA_{50} response calculations: All subjects in the trial will be considered either a responder or non-responder based upon the meeting of the primary endpoint based upon the definition above. For each patient, the DNA mutations present in the tumor will be identified through Foundation Medicine sequencing and/or through Personal Genome Diagnostics plasma cell-free DNA analysis. Patients with a deleterious mutation in the pre-specified gene list (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or other DNA repair genes) will be considered biomarker positive. For biomarker positive and biomarker negative subjects, we will calculate response rates with confidence intervals for hypothesis generation. Separate calculations for each testing modality will occur.
ii. Development of gene signature for response: based upon the responders and the DNA mutations identified through sequencing, a discovery of a biomarker set will take place with grouping of mutations associating with response.
iii. RNA expression profile signature positive and negative PSA_{50} response calculations: Similarly to above, subjects will have tumor tested with RNA expression profiling and scored for likelihood for response to olaparib per the Decipher GRID platform (GenomeDx). For subjects considered to have a positive RNA expression signature based upon a binary score assigned via the GenomeDx proprietary algorithm, a PSA_{50} response rate will be calculated. Similarly, a calculation will be performed for subjects considered to have a negative RNA expression signature.
iv. PARP-1 and γH2AX protein levels: Subjects will have prostatectomy samples analyzed for baseline PARP-1 and γH2AX proteins, and scored for positivity by immunohistochemistry on scale of 0 (none) to 3 (intense staining), and the results will be associated with responses for both proteins, separately.
v. Metastasis-free survival analysis: the median MFS will be estimated using the Kaplan-Meier method.
vi. Time to next anti-cancer therapy analysis: similarly to MFS, this time to event analysis will be estimated using the Kaplan-Meier method.

(f) Sample size justification: The study will enroll up to 50 subjects. The design is a multi-stage adaptive design, with stage sizes and decision rules calculated based upon assumptions for hypothesis testing for the primary endpoint.

The sample sizes for each stage are chosen to allow for interim assessment of the primary endpoint, in order to adapt if the unselected population results are suggestive of futility. In the case of futility in the all-comer population, a biomarker-selected stage can proceed. The operating characteristics of the design were assessed in a 10,000-iteration simulation, assuming biomarker prevalence is 10-15%. This design will have 0.90-0.91 power for the unselected population and a 0.79-0.80 power for the biomarker-selected population when no effect in the selected population. The overall type 1 error is 0.1 – 0.11, . The type 1 error for the biomarker-selected population is 0.04. The trial will also employ an early stopping rule for an AE of special interest. If >1 patient is diagnosed with myelodysplastic syndrome or acute myeloid leukemia during the trial, then the trial is to be stopped.
Funding, Regulatory, and Feasibility Issues: AstraZeneca is providing funding for performance of the clinical trial as well as providing olaparib to patients. IND will be filed and held by the principle investigator, Dr. Handy Marshall.
Patient Acceptability/Ethics and Consent Issues: This trial will be an alternative option for intervention other than standard therapies of ADT or surveillance. Olaparib has rare but life threatening side effects including MDS/AML in <1% of patients treated; by monthly laboratory monitoring and exclusion of patients with prior chemotherapy, we aim to minimize this risk. Additionally, by performing this trial in the highest risk patients with biochemically recurrent prostate cancer and by exclusion prior DNA-damaging chemotherapy, the potential benefits of a new therapy option with olaparib is more likely to outweigh risks, than if this trial were performed in patients with less risk for morbidity and mortality from prostate cancer.

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1. Introduction

1.1 Disease Background

Prostate cancer is the most commonly diagnosed non-cutaneous malignancy in men, with an estimated 180,000 cases annually in the United States [1]. It is the second most common cause of cancer mortality in the United States as well, with over 26,000 deaths in 2016 [1]. The discrepancy between the incidence and mortality numbers demonstrate its potential curability if treated while disease is local, as well as the non-lethal nature of some cancers, even if not treated definitively. While many men are cured of their disease, many others will unfortunately progress to incurable and lethal metastatic disease.

1.1.1. Clinical States of Prostate Cancer

The course of prostate cancer from diagnosis to death has been described as a series of distinct clinical states (See Figure 1.). These states are defined by the extent of disease and status of responsiveness to hormonal therapy. Therapies have been developed for specific states, as each state presents unique risks to the patient and different responsiveness of the disease to therapy.

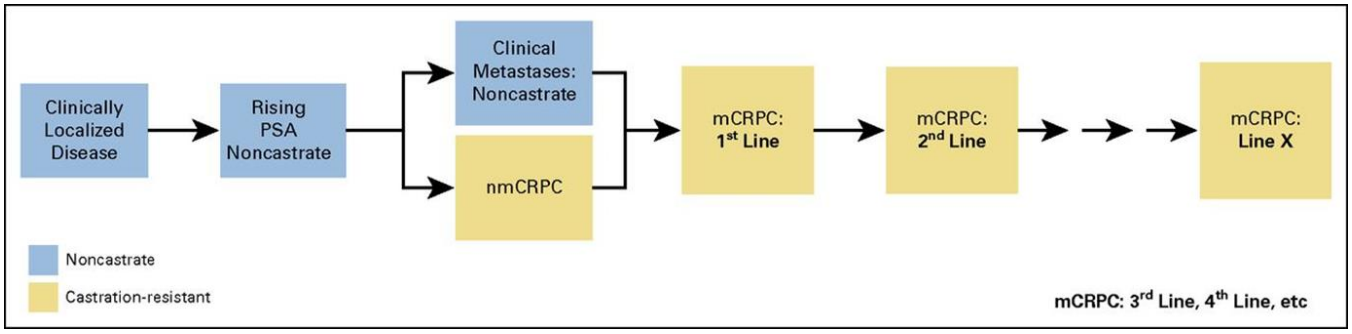

Figure 1. Clinical states of prostate cancer [2]

1.1.2. The Biochemically Recurrent Disease State

For patients who have undergone definitive local therapy for prostate cancer, for example with a radical prostatectomy, the first signs of recurrent disease are biochemical in nature. For such a patient who develops detectable prostate specific antigen (PSA), defined as confirmed values ≥0.2 for patients s/p prostatectomy, the clinical state is known as biochemically recurrent prostate cancer [3]. This state is further characterized by the lack of evidence of metastatic prostate cancer on traditional imaging, including CT scans of the abdomen and pelvis and NM bone scans of the skeleton. Salvage radiation therapy is potentially curative in some patients with biochemical recurrence [4].

For patients who were not candidates for salvage radiation therapy or who experience a rising PSA despite that therapy, their natural history will vary significantly depending on the clinical characteristics of the cancer. The risk of development of metastasis (and thus potentially lethal prostate cancer) has been shown to be dependent on multiple longitudinal

clinical characteristics [5]. Two of these clinical criteria are Gleason score sum and rate of rise of the PSA—the PSA Doubling time (PSADT). Based upon registry data for hundreds of patients who were treated with radical prostatectomies for localized prostate cancer, and subsequently experienced biochemical recurrence, nomograms have been constructed regarding the risk of developing metastatic disease based upon the Gleason score and/or PSADT. One of the largest cohorts observed was the Johns Hopkins cohort, wherein patients with biochemical recurrence were observed (without hormonal therapy) until the development of radiographic or clinical metastasis, thus demonstrating the natural history of the disease [6].

1.1.3. High Risk Patients with Biochemically Recurrent Prostate Cancer by PSADT

In the Hopkins cohort of 450 patients, patients with PSADT > 9 months rarely developed metastasis in first 5-years of follow-up [6]. In fact, the median metastasis-free survival for patients with PSADT 9-15 months and PSADT >15 months was 13 and 15 years, respectively. On the other hand, patients with PSAT < 9 months did have significant risks for development of clinical metastasis. The median metastasis-free survival for patients with PSADT <3 months and 3-9 months was 1 and 4 years, respectively, with the vast majority of these patients developing clinical metastasis within 5 years of follow-up.

These numbers were further refined with a recent expanded analysis that was inclusive of the Hopkins cohort and Department of Defense's Center for Prostate Disease Research database, those patients with PSADT < 6 months truly represented the high risk group [7]. In that study, with PSADT of 3-6 months developed distant clinical metastasis with twice the risk compared to those with PSADT 6-9 months by 5 years. Patients with PSADT <3 months had an even higher risk development of metastasis (Hazard Ratio of 2.4 compared to the group with PSADT 6-9 months).

1.2 Treatment Background

1.2.1 Description and mechanism of action

PARP functions in the DNA repair pathway, specifically by serving in base excision repair of DNA single strand breaks. Inhibition of PARP results in inability for cells to repair single strand breaks. Cells normally would employ the error-free homologous recombination pathway to repair such defects. However, in tumors that harbor defects in these DNA repair genes (such as BRCA1/2), the strand breaks lead to chromosomal instability and eventually cell death [8]. Olaparib functions in cells to inhibit various isoforms of PARP.

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 ovarian 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.

BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo [9, 10] and in the clinic [11]. The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair [12, 13]. Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

Olaparib is FDA-approved for the treatment of ovarian cancer patients who have progressed after three or more prior lines of therapy and harbor known or suspected deleterious mutations in BRCA1 or BRCA2 [14]. It has been studied in limited fashion in patients with advanced prostate cancer.

In addition to its efficacy in BRCA1 and BRCA2 defective tumors, Olaparib has been demonstrated to bind the PARP protein thus trapping it on DNA [13]. This other mechanism is believed to generate further cytotoxicity to cancer cells, as multiple other cellular pathways (beyond homologous recombination) are needed to remove the trapped protein and restore DNA integrity.

1.2.2 Preclinical Studies

The pre-clinical experience is fully described in the current version of the olaparib Investigator's Brochure (IB).

Olaparib has demonstrated in vitro and in vivo efficacy in preclinical studies in certain prostate cancer cell lines. The study of Brenner et al. tested VCaP cells in vitro and as xenografts and demonstrated efficacy of olaparib monotherapy compared to controls [15]. Efficacy in 22Rv1 cell line xenografts was similarly seen with olaparib in a separate study [16]. Other cell lines were not sensitive in preclinical studies. These included PC3 cells [15] and LNCaP cells [17].

1.2.3 Clinical Studies in Prostate Cancer

Clinical experience with olaparib is fully described in the current version of the olaparib Investigator's Brochure.

Small numbers of advanced prostate cancer patients were included in initial clinical studies of olaparib. In the initial phase I report on olaparib, 3 patients with prostate cancer were included [11]. In a follow-up study of patients with germline BRCA mutations, 8 prostate cancer patients were included [18].

Recently, a larger cohort of prostate cancer patients treated with olaparib was published [19]. Patients were treated with the FDA-approved dose of 400mg by mouth twice daily. In the trial, 50 patients were enrolled. Three patients discontinued olaparib due to adverse events. There were 30 adverse events of grade 3-4 level. Grade 3-4 events occurring in greater than 1 patient were anemia (20%), fatigue (12%), leukopenia (6%), neutropenia and thrombocytopenia (4%).

Of the patients in the study, 16 were identified to have a mutation in DNA repair genes (BRCA1, BRCA2, ATM, FANCA, CHEK2, PALB2, HDAC2, RAD51, MLH3, ERCC3, MRE11, or NBN) [19]. Eleven of 49 evaluable patients experienced a greater than 50% decline in PSA (a PSA50 response). Six patients achieved a partial radiographic response by RECIST criteria. Every patient with a radiographic response also had a PSA50 response. Of these 11 responders in the study, 10 were among the patients with the mutations in the tested DNA repair genes. One responder was among the remaining 33 without an identified mutations.

There are currently no studies published in hormone sensitive prostate cancer patients.

1.2.4 Clinical Studies in All Diseases

The toxicology and safety pharmacology is fully described in the current version of the olaparib Investigator's Brochure (IB).

The largest pool of data for olaparib is drawn from a phase II trial of patients with germline delirious BRCA 1 or 2 mutations [18]. That study included 298 patients, including 193 with ovarian cancer and 62 with breast cancer. The analysis of the ovarian cancer cohort in this study led to the FDA-approval of olaparib. The overall tumor response rate by RECIST criteria was 26.2% across all tumor types. Specifically for the ovarian cancer cohort, the median response duration was 7.9 months.

Adverse events were reported in the trial and are summarized below:

Adverse Event	Any Grade Toxicity	Grade 3-4 Toxicity
Fatigue	59.1%	6.4
Nausea	59.1%	0.3
Vomiting	37.2%	2.3
Anemia	32.9%	17.4
Diarrhea	27.2%	1.3
Abdominal Pain	25.8%	5.7
Decreased Appetite	20.8%	0.3
Dyspepsia	17.4%	0.0
Headache	16.1%	0.3
Dysgeusia	15.8%	0.0

Table 1. Events occurring in >15% (any grade) or >5% (grade 3-4) in the trial [18].

Severe rare but serious adverse events have been cataloged in clinical trials to this point. In the Kaufman study, 6 (2%) of patients developed myelodysplastic syndrome or acute myeloid leukemia. Of all 2618 patients treated with olaparib on clinical trials, 22 (<1%) developed MDS or AML; however, the occurrence was fatal in most cases (per the investigators brochure). Pneumonitis also was seen to occur in <1% of patients.

1.3 Rationale for olaparib in high risk biochemically recurrent prostate cancer

1.3.1 DNA repair defects are common in prostate cancer

Several large studies have been recently published cataloging the genetic mutations that are present in prostate cancer. The TCGA examined 333 primary prostatectomy specimens that were collected without selection for risk group or Gleason grade [20]. In that analysis, inactivating mutations in DNA repair genes were identified in 19% of samples. By prevalence, these genes identified were FANCD2 (7%), ATM (4%), BRCA2 (3%), RAD51C (3%), CDK12 (2%), and BRCA1 (1%). Specifically looking at the genes identified in the Mateo study (BRCA1, BRCA2, ATM, FANCA, CHEK2, PALB2, HDAC2, RAD51, MLH3, ERCC3, MRE11A, NBN) [19], the prevalence was 9%.

A similar analysis of the genetic mutations was performed in a cohort of 150 samples from patients with metastatic castration-resistant prostate cancer [21]. In that study, the authors identified 23% of patients harbored mutations in DNA repair genes. Most frequently mutated DNA repair genes were BRCA2 (13.3%), ATM (7.3%), and CDK12 (4.7%). Again using the Mateo study's list of genes, the prevalence of mutations was 18%.

A final study to discuss regarding the prevalence of DNA repair defects in prostate cancer is a recent analysis of the prevalence of germline mutations in patients with prostate cancer [22]. That study examined 692 patients with metastatic prostate cancer and tested for germline mutations in 20 DNA repair genes. Overall 11.8% of patients were found to have germline DNA repair mutations. The most commonly mutated genes were BRCA2 (5.3%), CHEK2 (1.9%), ATM (1.6%), BRCA1 (0.9%), RAD51D (0.4%), and PALB2 (0.4%). The authors compared the frequencies of mutations to those present in 499 with localized prostate cancer. In the localized prostate cancer cohort, the prevalence was lower at 4.6%. Of note, the baseline prevalence for these mutations in the general population is 2.7%.

These studies demonstrate that DNA repair mutations are relatively common in prostate cancer, and are more common in metastatic prostate cancer than in localized prostate cancer. Based upon these large genomic analyses for cohorts of patients with prostate cancer, we establish a range of likely prevalence for DNA repair defective tumors for patients with biochemically recurrent prostate cancer. For mutations detectable in tumor tissue, the prevalence for biochemically recurrent patients likely falls between the 19-23% range per TCGA and SU2C data (9-18% for those genes from the Mateo study). The anticipated range for germline mutations is 4.6-11.8% per the Prichard analysis.

Yet, despite some encouraging preliminary data on a mutation signature that is predictive of response to olaparib, the optimal biomarker profile for response is probably not known at this time. This is in fact demonstrated in the Mateo study, in which one patient without a known genetic defect in the analyzed genes achieved an 88% PSA response, a partial response per RECIST criteria, and a duration of response of at least 44 weeks at the time of publication.

1.3.2 Rationale for conducting study

There are several pending trials are being conducted with olaparib for patients with metastatic CRPC, including olaparib as monotherapy (NCT01682772) and olaparib in combination with enzalutamide (NCT02500901). The FDA recently announced breakthrough designation for olaparib for metastatic CRPC, refractory to novel hormone

therapy and chemotherapy, with mutations in BRCA1, BRCA2, or ATM. While PARP inhibition is showing promise in these initial studies, reserving its use for end-stage patients may not be the optimal timing for olaparib therapy in some patients. PARP inhibition has not been tested in earlier disease states for prostate cancer.

Olaparib may be an ideal therapy for men with biochemically recurrent prostate cancer. PARP inhibition with olaparib in this earlier disease state may be more effective in hormone-sensitive prostate cancer (rather than in heavily pre-treated/resistant tumors), as tumor heterogeneity may be significantly lower. In addition, it is unknown whether genetic changes identified in prostatectomy specimens will be predictive of response to olaparib. PARP inhibition may also be active in ways beyond the DNA repair pathway for prostate cancer. This trial will attempt to test questions regarding the activity of olaparib in hormone-naïve prostate cancer and explore associations between responses with genetic mutations and expression profiles identified in the primary prostatectomy specimens.

In this trial, subjects will be enrolled with biochemically recurrent prostate cancer. Patients will be required to have undergone prior definitive radical prostatectomy with tissue available for analysis. Patients will also have required to have previously been treated with salvage radiation therapy, declined salvage radiation therapy, or were not candidates for salvage radiation. By requiring prior definitive therapy and attempted salvage therapy, the enrolled patients are those that are not felt to have known curative options remaining for their cancer.

Furthermore, patients are required to have high risk for development of metastatic disease, specifically by requiring a PSADT < 6 months. This selects for patients who have a high risk of suffering morbidity and mortality from prostate cancer in the future. Given the potential toxicity of any treatment in this space, weighing that risk with a potential benefit is important and thus is the rationale for limiting enrollment to those patients with rapid PSADT.

The current standard of care treatments for patients with high risk biochemically recurrent prostate cancer are either observation or ADT [23]. ADT has not been shown to provide a survival benefit in this setting, and the decision to initiate ADT will depend on patient preference and perceived risks of the disease. A non-hormonal therapy such as olaparib would provide an alternative to ADT as a potential treatment option for these patients.

The study is an open-label single arm phase II study. Enrolled subjects will be treated with olaparib 300mg by mouth twice daily until progression or toxicity requiring cessation. Patients will be assessed at least monthly for toxicity, including laboratory investigations. Because an alternative standard approach for these patients is observation (and continued PSA rise with a similar doubling time in >95% of patients), an inactive compound in this space would be expected to provide a 5% or less response rate, which would be the same as observation for these patients. It is in that context that a single arm study is being conducted rather than randomized placebo-controlled study. Among data to be collected include monthly PSA values, toxicity assessments, duration of olaparib therapy, and correlative investigations. The correlative studies include multiple studies using tumor tissue from the explanted prostate tumors: genomic mutation analysis, RNA expression profiling, and baseline PARP-1 and γH2AX protein levels.

1.3.3 Rationale for dose selection

Olaparib will be administered at a dose of 300mg by mouth twice daily in tablet formulation. This dose is similar in terms of safety and efficacy to the FDA-approved dose of 400mg by mouth twice daily in capsule formulation. This dose was established in the phase I studies and was also employed in prior studies involving prostate cancer.

1.3.4 Rationale for correlative studies

1.3.4.1 Genetic mutation analysis in tumor

Tumors will be analyzed using the FoundationOne platform by Foundation Medicine (Cambridge, MA). This test sequences provides mutation analysis in 315 selected genes and rearrangement analysis in 28 genes. The genes include those commonly mutated (BRCA2, ATM, BRCA1, CHEK2, CDK12, RAD51, PALB2, FANCL). The analysis provides a depth of coverage of 500X, and is reported by variant analysis with regard to likely pathogenicity. By cataloging the mutations present in the primary tumors for subjects in the study, correlative analysis associating response with specific mutations can be performed. The testing will be inclusive of a sub-panel of genes of particular interest (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and other DNA repair genes).

1.3.4.2 RNA expression array analysis in tumor

An alternative possibility for tumor sensitivity to olaparib is through epigenetic gene expression changes that may not be identified through genetic mutation analysis alone. In conjunction with the DNA mutation testing planned to be performed through Foundation Medicine, subjects will have tissue tested for RNA expression arrays for associating response to olaparib. For this assay, samples will be tested by GenomeDx (San Diego, CA) using the Decipher GRID microarray platform. The gene expression profile will be inclusive of a metastasis signature and olaparib-sensitivity signature. The metastatic signature has been validated in a cohort of patients with high risks for recurrence after primary prostate cancer therapy [24, 25], as well as in a cohort of patients undergoing salvage radiation therapy after biochemical recurrence of prostate cancer [26]. A post-hoc analysis will be performed to evaluate these signatures, and further determine a gene expression profile that predicts response to olaparib.

1.3.4.3 PARP-1 and γH2AX protein levels in tumor

Beyond the underlying genetic mutations in DNA repair genes and the associated RNA expression profiles, we are exploring whether baseline assessment of the PARP-1 enzyme or γH2AX protein positivity by immunohistochemistry is predictive of response. γH2AX is a protein that serves as a marker for double strand DNA breaks. PARP-1 is the primary molecular target for olaparib.

2. OBJECTIVES

2.1 Primary Objective

The primary objective is to estimate the response rate (PSA_{50}) to olaparib for patients with high-risk biochemically-recurrent prostate cancer. By estimating the PSA_{50} response rate, this will serve as an initial exploration of olaparib's activity in this disease state.

2.2 Secondary Objectives

•To determine the safety/tolerability of olaparib in the biochemically-recurrent prostate cancer patient population.
•To estimate the median PSA progression-free survival.
•To estimate the median time to PSA doubling from baseline.
•To estimate the rate of durable undetectable PSA in patients responding to olaparib.

2.3 Correlative/Exploratory/Tertiary Objectives

•*(if an enriched population is not accrued)* To estimate PSA_{50} response in "biomarker positive" patients, based upon FoundationOne tissue-based mutations in the pre-specified gene list (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or other DNA repair genes).
•*(if an enriched population is not accrued)* To estimate PSA_{50} response in "biomarker negative" patients, based upon tissue-based mutations in the pre-specified gene list.
•To estimate PSA_{50} response rate for patients with and without a mutation on the pre-specified list, based upon plasma cell-free DNA analysis using the pre-specified gene list.
•To develop a genetic mutation signature associated with response to olaparib. For this objective, the biomarker signature will not be defined *a priori* but instead this will involve an exploratory analysis.
•To develop an RNA expression signature associated with response to olaparib.
•To investigate any association between PARP-1 and γH2AX protein levels in tumor with response to olaparib.
•To estimate median metastasis-free survival.
•To estimate median time to next anti-cancer therapy.

3. PATIENT SELECTION

3.1 Target Population

The target population is men with prostate cancer who have experienced a rising PSA (biochemical recurrence) after definitive local therapy with a radical prostatectomy. This population will not have evidence of metastatic disease on CT scan and NM bone scan. Furthermore, the population will be high risk for development of metastatic disease, as defined by a PSA doubling time (PSADT) of < 6 months and an absolute PSA value of ≥1.0 ng/ml.

3.2 Expected Enrollment

A total of 50 patients will be included in this study. The first patients are expected to be enrolled in March 2017. Accrual is expected to be completed in 24 months, or earlier, once the protocol has been approved by the IRB at each participating institution.

3.3 Inclusion Criteria

To be included in this study, patients should meet all of the following criteria:

- Willing and able to provide written informed consent and HIPAA authorization for the release of personal health information. Provision of informed consent prior to any study procedures.

  NOTE: HIPAA authorization may be either included in the informed consent or obtained separately.

- Males aged 18 years of age and above
- Histological proof of adenocarcinoma of the prostate
- Prior local therapy with prostatectomy required, with available tissue from prostatectomy specimen to send for genomic and transcriptomic testing. Specifically, either FFPE blocks or 35-40 unstained slides from the primary prostatectomy specimen will need to be available for central pathologic review and processing.
- Prior salvage or adjuvant radiation therapy is allowed but not mandated. Radiation therapy must have been completed for at least 6 months.
- Absolute PSA ≥1 ng/ml. Prior undetectable PSA post-prostatectomy is not required.
- PSADT ≤6 months, based upon ≥3 consecutive measurements collected in the past 12 months, at least 4 weeks apart, calculating using the MSKCC calculator (https://www.mskcc.org/nomograms/prostate/psa-doubling-time)
- No radiographic evidence of metastatic disease by CT scan and bone scan, performed within the prior 4 weeks.
- Serum testosterone ≥ 150 ng/dl.
- Participants 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 ≥ 75 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

      Note: Patients with elevations in bilirubin, AST, or ALT should be thoroughly evaluated for the etiology of this abnormality prior to entry and patients with evidence of viral infection should be excluded.

    - Participants must have creatinine clearance estimated using the Cockcroft-Gault equation of ≥51 mL/min:

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

      Note: Patients with creatinine clearance between 51- 80 mL/min either at trial enrolment or during the course of the trial should be monitored every 2 weeks for laboratory assessment and toxicity evaluation.

- ECOG PS ≤ 1. (Appendix A: Performance Status Criteria)
- Participants must have a life expectancy ≥ 16 weeks.

- Male participants and their partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination [see appendix E for acceptable methods], throughout the period of taking study treatment and for 3 months after last dose of study drug to prevent pregnancy in a partner.
- *For enrichment stage of trial only (if necessary)*: Confirmation of a suspected/known deleterious mutation in a gene of interest (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or other DNA repair genes) via CLIA certified testing.

3.4 Exclusion Criteria

Patients that meet any of the criteria listed below will not be eligible for study entry:

- Metastatic disease or currently active second malignancy
- Prior ADT in the past 6 months. Prior ADT in context of neoadjuvant/adjuvant primary; prior ADT for biochemical recurrence is allowed, as long as no ADT has been administered in past 6 months and testosterone has recovered (>150 ng/dl). The total duration of prior ADT should not exceed 24 months.
- Prior oral anti-androgen (e.g. bicalutamide, nilutamide, enzalutamide, apalutamide), or androgen synthesis inhibitor (e.g. abiraterone, orteronel) in the past 6 months. 5-alpha reductase inhibitor therapy (e.g. finasteride, dutasteride) is allowed, as long as subject has been stable on medication for past 6 months.
- Prior treatment with intravenous chemotherapy.
- Use of any prohibited concomitant medications (Appendix B: Medications With the Potential for Drug-Drug Interactions) within the prior 2 weeks.
- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
- Previous enrolment in the present study
- Participation in another clinical study with an investigational product during the last 1 month.
- Any previous treatment with PARP inhibitor, including olaparib.
- Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome
- 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. During the study, if co-administration of a strong or moderate inhibitor is required because there is no suitable alternative medication, exception to this criterion may be allowed with a suitable dose reduction of olaparib (see section 5.5.2.1)
- Concomitant use of known strong CYP3A inducers (eg. phenobarbital, 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 phenobarbital and 3 weeks for other agents.

- Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia.
- Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML.
- Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
- 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, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.
- Unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
- Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV).
- Known hypersensitivity to olaparib or any of the excipients of the product.
- Known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids
- Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no.10)

4. PATIENT REGISTRATION AND ENROLLMENT PLAN

4.1 Registration Procedure

After eligibility screening and confirmation that a patient is eligible, patients who are selected to participate will be registered with the Lead Center Johns Hopkins, with their local study site/institution, and if applicable, in the online centralized PCCTC database. A record of patients who fail to meet entry criteria (ie, screen failures) will be maintained. Patient registration must be complete before beginning any treatment or study activities. A complete, signed study consent and HIPAA consent are required for registration.

4.1.1 Registration at Johns Hopkins

Confirm eligibility as defined in ***Section***

•***(if** an enriched population is not accrued)* To estimate PSA50 response in "biomarker positive" patients, based upon FoundationOne tissue-based mutations in the pre-specified gene list (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or other DNA repair genes).

•*(if an enriched population is not accrued)* To estimate PSA50 response in "biomarker negative" patients, based upon tissue-based mutations in the pre-specified gene list.
•To estimate PSA50 response rate for patients with and without a mutation on the pre-specified list, based upon plasma cell-free DNA analysis using the pre-specified gene list.
•To develop a genetic mutation signature associated with response to olaparib. For this objective, the biomarker signature will not be defined *a priori* but instead this will involve an exploratory analysis.
•To develop an RNA expression signature associated with response to olaparib.
•To investigate any association between PARP-1 and γH2AX protein levels in tumor with response to olaparib.
•To estimate median metastasis-free survival.
•To estimate median time to next anti-cancer therapy.

3. Patient Selection.

Obtain informed consent, by following procedures in ***Section 11.3 Written Informed Consent***.

Patient will be entered into CRMS system and enrolled in trial.

4.1.2 Multicenter/Participating site registration
Central registration for this study will take place at Johns Hopkins.

Patient registration at each study site/institution will be conducted according to the institution's established policies. Before registration, patients will be asked to sign and date an Institutional Review Board (IRB)-approved consent form and a research authorization/HIPAA form. Patients must be registered with their local site/institution and also with the sponsor or Lead Site before beginning any treatment or study activities.

5. TREATMENT/INTERVENTION PLAN

The following assessments and procedures will occur during the study. A schedule of assessments is provided in Table 2.

Table 2 Study Calendar

	Prestudy	Study Period				
		On Treatment Assessments (Every 28 days)				Off Treatment / Follow-up
	Day -7[a,h] (±7days)	C1D1[d,h] (±3 d)	C2D1[d h] (±3 d)	C3D1[h] (±3 d)	CnD1[h] (±3 d)	Every 28 days [e,h] (±3 d)
Informed consent	X					
Demographics	X					
Complete Medical history	X					
EKG	X					
Interval Medical history		X	X	X	X	X
Physical exam	X	X	X	X	X	X
Vital signs (P, BP, RR, T)	X	X	X	X	X	X
Height	X					
Weight	X	X	X	X	X	X
ECOG Performance status	X		X	X	X	X
Toxicity assessment	X		X	X	X	X
Concomitant meds	X	X	X	X	X	X
Histologic confirmation and Tissue/DNA studies	X[f]					
Radiologic tests[b]	X				X[b]	X[b]
Laboratory tests[c]	X	X[g]	X	X	X	X
Olaparib		X	X	X	X	
Adverse events			X	X	X	X

Abbreviations: CBC, complete blood count; CT, computerized tomography; MRI, magnetic resonance imaging; PSA, prostate-specific antigen

a Informed consent and radiologic assessments should be obtained within 4 weeks of study start date.

b Radiographic evaluations (CT A/P and NM Bone Scan every 6 months while enrolled in the study). They are needed within 28 days of screening; if previously performed then they are to be performed at screening. CT A/P and NM Bone Scan are to be performed at off-treatment visit if they have not been performed in the prior 3 months.

c CBC w/diff, Complete Metabolic Panel, PSA at each visit. Testosterone, PT/INR, PTT, and Urinalysis at screening visit only. Note: Patients with creatinine clearance between 51- 80 mL/min either at trial enrolment or during the course of the trial should be monitored every 2 weeks for laboratory assessment and toxicity evaluation.

d For Cycle 1 and Cycle 2, CBCs will be repeated weekly.

e Subjects will be followed after completion of olaparib therapy monthly until toxicities resolve to grade 0-1.

f Tissue from prostatectomy sent to Foundation Medicine and GenomeDx

g C1D1 routine labs (CBC w/diff, Comprehensive Metabolic Panel, PSA) are only required if >7 days since screening labs.

H In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for inperson clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in

Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

5.1 Screening/Pretreatment Assessment (Day -7 ±7 days)

Before initiating any screening activities, the scope of the study should be explained to each patient. Patients should be advised of any known risks inherent in the planned procedures, any alternative treatment options, their right to withdraw from the study at any time for any reason, and their right to privacy. After this explanation, patients should be asked to sign and date a Notice of Privacy Practice research authorization/HIPAA form and an IRB-approved statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50).

- The screening visit will determine patient eligibility according to the inclusion and exclusion criteria (Sections 3.3Inclusion Criteria & Histological proof of adenocarcinoma of the prostate
- Prior local therapy with prostatectomy required, with available tissue from prostatectomy specimen to send for genomic and transcriptomic testing. Specifically, either FFPE blocks or 35-40 unstained slides from the primary prostatectomy specimen will need to be available for central pathologic review and processing.
- Prior salvage or adjuvant radiation therapy is allowed but not mandated. Radiation therapy must have been completed for at least 6 months.
- Absolute PSA ≥1 ng/ml. Prior undetectable PSA post-prostatectomy is not required.
- PSADT ≤6 months, based upon ≥3 consecutive measurements collected in the past 12 months, at least 4 weeks apart, calculating using the MSKCC calculator (https://www.mskcc.org/nomograms/prostate/psa-doubling-time)
- No radiographic evidence of metastatic disease by CT scan and bone scan, performed within the prior 4 weeks.
- Serum testosterone ≥ 150 ng/dl.
- Participants 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 ≥ 75 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

      Note: Patients with elevations in bilirubin, AST, or ALT should be thoroughly evaluated for the etiology of this abnormality prior to entry and patients with evidence of viral infection should be excluded.

    - Participants must have creatinine clearance estimated using the Cockcroft-Gault equation of ≥51 mL/min:

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

Note: Patients with creatinine clearance between 51- 80 mL/min either at trial enrolment or during the course of the trial should be monitored every 2 weeks for laboratory assessment and toxicity evaluation.

- ECOG PS ≤ 1. (Appendix A: Performance Status Criteria)
- Participants must have a life expectancy ≥ 16 weeks.
- Male participants and their partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination [see appendix E for acceptable methods], throughout the period of taking study treatment and for 3 months after last dose of study drug to prevent pregnancy in a partner.
- *For enrichment stage of trial only (if necessary)*: Confirmation of a suspected/known deleterious mutation in a gene of interest (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or other DNA repair genes) via CLIA certified testing.

3.4 Exclusion Criteria). The following assessments will be performed at this visit:

- obtain informed consent and research authorization
- record demographics (including age) and medical history (including prior treatment for prostate carcinoma)
- conduct physical exam (including vital signs, height/weight)
- obtain history regarding prior treatment history for prostate cancer (including history of ADT, history of radiation therapy or other local therapy, and prior PSA history to calculate PSADT).
- obtain histologic confirmation of disease, and radiographic evidence of lack of metastatic disease. If radiographic studies have not been performed in prior 4 weeks, they must be obtained as part of screening.
- perform laboratory tests: Complete blood count w/Diff, PSA, Comprehensive metabolic panel, urinalysis, PT/INR, PTT, testosterone.
- PSA doubling time will be confirmed using MSKCC calculator (https://www.mskcc.org/nomograms/prostate/psa-doubling-time)
- assess performance status (ECOG). (Appendix A)
- Perform 12-lead EKG. ECGs are required within 7 days prior to starting study treatment and when clinically indicated.
    - Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

  - ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

- determine suitability for olaparib therapy
- discuss concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)
- *For enrichment stage of trial only (if necessary)*: obtain next generation genetic sequencing of tumor by tissue analysis of primary prostatectomy specimen via Foundation Medicine platform. Confirmation of a mutation in a gene of interest is necessary prior to proceeding with enrollment. If a patient previously underwent either somatic or germline testing and provide documentation of a mutation in a gene of interest, then enrollment can proceed. The list of genes of interest: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or other DNA repair genes.

Relevant information should be documented. The institutional registration should be finalized, and appropriate documents (ie, signed informed consent, research authorization/HIPAA form, and supporting source documentation for eligibility questions) faxed or emailed to the lead site/sponsor. A copy of the informed consent should also be forwarded to the PCCTC coordinating center.

Information for patients who do not meet the eligibility criteria to participate in this study (ie, screening failures) should be captured in consortium database at the pretreatment assessment.

For any subject that has a DNA repair gene mutation identified in tumor or cell-free DNA testing, the subject will be referred to medical genetics for counseling and consideration of further targeted testing to determine if the identified mutation is present in the germline.

5.2 Treatment/Intervention Period (Day 1 of each 28 day cycle ± 3 Days, ongoing)

Patients will be seen on D1 of each cycle of olaparib (consisting of 28 days, +/- 3 days). The following assessments will be performed at each visit:

- conduct physical exam (including vital signs, weight)
- obtain any medical history changes from prior assessment
- assess performance status (ECOG). (Appendix A)
- review concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)

5.3.1 Clinical, laboratory, and radiographic assessments

On Day 1 of each cycle, patients will have a non-fasting blood drawn for the following values: Repeat labs are not needed on C1D1 as long as visit is within 7 days of screening values.

- CBC. For Cycle 1 and Cycle 2, CBCs will be repeated weekly

- Comprehensive chemistry panel
- PSA
- Research Blood Draw for FoundationACT will occur once during study on C1D1.

Note: Patients with creatinine clearance between 51- 80 mL/min either at trial enrolment or during the course of the trial should be monitored every 2 weeks for laboratory assessment and toxicity evaluation.

Every 6 cycles, patients will have radiographic studies:

- CT Abdomen and Pelvis with contrast
- NM Bone scan

Laboratory Safety Assessments:

Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials. Coagulation [activated partial thromboplastin time (APTT) and international normalized ratio (INR)] will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Biochemistry assessments for safety (sodium, potassium, calcium, fasting glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin.

Urinalysis by dipstick should be performed at baseline and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities as defined in *Section 5.5.2.1. Dose Modifications for Toxicities*.

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix F 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions

5.3.2 Handling pathologic materials

Pathology will be reviewed and processed centrally at Johns Hopkins. RP specimens will be handled and sampled in a uniform fashion.

5.3.3.1. Tissue processing for DNA Mutation Analysis

FFPE blocks will be sent to lead pathologist at Johns Hopkins for processing. 10 unstained slides and 1 H&E slide, representative of underlying tumor, will be prepared for FoundationOne testing. Tumor tissue on slides are optimally 25mm^2 in area and 4-5 microns thick.

5.3.3.3. Tissue processing for RNA Expression Analysis

FFPE blocks will be assessed for representative tumor tissue and two 1.5mm punches will be collected using the disposable biopsy punch tool. Punch specimens will be placed in microcentrifuge tubes and stored at 4C until shipping to GenomeDx. In the case that FFPE blocks are not available, 15 unstained slides will be employed to create the samples.

5.3.3.4. Tissue processing for PARP-1 and γH2AX Protein Analysis

10 unstained slides from the FFPE tissue block will be prepared. Tumor tissue will be sent to the Schiewer laboratory (Thomas Jefferson, Philadelphia, PA) for testing.

5.3.3.5 Optional Tissue Banking

For patients who have consented to allow banking of biospecimens for future research, 5 unstained slides from the FFPE tissue block will be prepared and banked for future research.

5.3.3 Safety assessments

Adverse events (AEs) will be monitored at each scheduled visit and throughout the study. Toxicity will be assessed using the most recent National Cancer Institute (NCI) guidance: the most recent version of Common Terminology Criteria for Adverse Events (CTCAE).

5.4 Treatment-Limiting Adverse Event

A treatment-limiting adverse event is any AE related to protocol therapy experienced during the study resulting in treatment termination. Such events include dose adjustments for each drug (ie, increases, decreases, delaying, or omitting therapy) related to the AE after therapy has been initiated or AEs because of other therapies, such as surgery and radiation therapy.

5.5 Dosing and Dose Modifications

5.5.1 Dosing

For all centers, olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Dosing containers will be supplied to contain sufficient medication for at least 28 days plus overage, in form of four 32-count bottles for the standard dose, for example. Olaparib will be dispensed to patients on Day 1 and every 28

days thereafter until the patient completes the study, withdraws from the study or closure of the study.

Study treatment is available as a film-coated tablet containing 150mg or 100mg of olaparib. 150mg tablets are supplied as the starting standard dose, and 100mg tablets are available if dose reduction is required.

Patients will be administered olaparib orally twice daily at 300mg bid continually. Two 150mg of olaparib tablets should be taken twice daily, approximately 12 hours apart with one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

If vomiting occurs shortly after the olaparib or placebo 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.

5.5.2 Dose Modifications

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 6. The NCI CTCAE 4.0 will be used to grade adverse events.

At each study visit for the duration of their participation in the study, patients will be evaluated for adverse events (all grades), serious adverse events (SAEs), and adverse events that require study drug interruption or discontinuation. Patients discontinued from the treatment phase of the study for any reason will be evaluated approximately 28 days after the last dose of the study drug.

5.5.2.1. Dose Modifications for co-administration of strong or moderate CYP3A inhibitors, if co-administration becomes necessary during the study.

Patients enrolled in the study are required to not be taking strong or moderate CYP3A inhibitors. However, if co-administration of a strong or moderate CYP3A inhibitor because necessary during the study, it is allowed only if there are no suitable alternative concomitant medication. If co-administration is thus required, the olaparib will be suitably dose-reduced, per the table below.

Table 3 Dose-modification: For patients requiring concurrent strong CYP3A inhibitors

Dose Level	Dose of Olaparib
Standard Dose	100mg by mouth twice daily
Reduction level 1	Hold Olaparib
Reduction level 2	Hold Olaparib

Table 4 Dose-modification: For patients requiring concurrent moderate CYP3A inhibitors

Dose Level	Dose of Olaparib
Standard Dose	150mg by mouth twice daily
Reduction level 1	100mg by mouth twice daily
Reduction level 2	100mg by mouth twice daily

A washout period is required after completion of therapy with the strong or moderate CYP3A inhibitor prior to re-escalation at original dose. If a strong inhibitor has been administered, the washout period is 5 half-lives of that drug. If a moderate inhibitor has been administered, the washout period is 3 half-lives of that drug.

5.5.2.2. Dose Modifications for concurrent 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.

For patients who develop moderate renal impairment (CLcr <50 mL/min), hold dose until recovery.
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 olaparib be discontinued.

5.5.2.3. Dose Modifications for Toxicities

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions.

Patients who require an interruption in olaparib for >2 weeks due to toxicity must discontinue study drug.

Adverse events possibly related to study drug must be resolved to grade 1 or baseline prior to resumption of dosing.

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 with the exception of cases of CTC grade 3 /4 anemia when dose should be reduced to 200 mg twice daily as first 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.

Management of hematological toxicity

Management of anemia

Table 5 Management of anaemia

Haemoglobin	Action to be taken
Hb < 10 *but* **≥ 8 g/dl (CTCAE Grade 2)**	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 2 weeks. If repeat Hb**< 10** *but* **≥ 8 g/dl**, dose interrupt (for max of 2 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step may be considered.
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 2 weeks until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce to **dose should be reduced to 200 mg twice daily as first step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment must be discontinued.**

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.

Management of neutropenia, leukopenia and thrombocytopenia

Table 6 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 2 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 2 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 Discontinue therapy in cases of febrile neutropenia and thrombocytopenia associated with hemorrhage

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.

Management of prolonged hematological toxicities while on study treatment

Discontinue olaparib 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)

Adverse events possibly must be resolved to grade 1 or baseline prior to resumption of dosing.

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 2 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. 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.

Bone marrow or blood cytogenetic analysis

Bone marrow or blood cytogenetic analysis may be performed according to standard hematological practice for patients with prolonged hematological toxicities. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to AstraZeneca Patient Safety for documentation on the Patient Safety database. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database. ***Management of non-haematological toxicity***

Dose interruptions are allowed as required, for a maximum of 2 weeks. Patients who require an interruption in olaparib for >2 weeks due to toxicity must discontinue study drug. Where toxicity reoccurs following re-challenge with study treatment, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg bid as a first step and to 200 mg bid 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.

Adverse events possibly related to study drug must be resolved to grade 1 or baseline prior to resumption of dosing.

Note. In case a patient shows an AST or ALT ≥3 ULN or total bilirubin ≥2 ULN please refer to Appendix F Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions. Potential Hy's Law cases (AST or ALT ≥3x ULN and TBL ≥2xULN with no other reason) must discontinue the study.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnoea) 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 Principle Investigator.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. 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 Principle 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 a 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 7 Dose reductions for study treatment

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

5.6 End of Treatment/Treatment Discontinuation Visit (28 days after last dose ±3 days)

- conduct physical exam (including vital signs, height/weight)
- perform laboratory tests: Complete blood count w/Diff, PSA, Comprehensive metabolic panel
- assess performance status (ECOG). (Appendix A)
- review concurrent medications
- assess AEs
- if patient is discontinuing participation in study, perform radiographic tests: CT A/P and NM Bone Scan (if these have not been performed in the prior 3 months)

5.7 Follow-up (At least every 28 days while active AEs)

Patients will be followed every 28 days beyond the end of treatment visit if they have withdrawn from study because of AEs. Patients withdrawn from the study because of AEs will be followed until the adverse event has either resolved or stabilized. Reasons for premature withdrawal should be determined and noted. To be performed at each visit will be:

- conduct physical exam (including vital signs, height/weight)
- perform laboratory tests (CBC w/diff, Comprehensive metabolic panel) only as indicated by AEs requiring follow-up
- assess performance status (ECOG). (Appendix A)
- review concurrent medications
- reassess AEs.

- When patient will discontinuing participation in study, perform radiographic tests: CT A/P and NM Bone Scan (if these have not been performed in the prior 3 months)

5.8 Correlative/Special Studies

5.8.1. DNA sequencing
The archival tissue from radical prostatectomy will be obtained by pathology at Johns Hopkins. A sample of tumor will be sent to Foundation Medicine for next generation sequencing, based upon their commercially available platform.

5.8.2. RNA expression profiling
A sample of tumor from the primary prostatectomy archival tissue will be sent to GenomeDx for RNA expression profiling.

5.8.3. PARP-1 and γH2AX Protein Analysis
A sample of tumor will be send to the Schiewer laboratory for testing.

5.9 Concomitant Medications

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the case report form (CRF).

Medications that may NOT be administered:

- No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.
- Live virus and live bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

Restricted concomitant medications

Strong or Moderate CYP3A inhibitors

Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib. During the study, if co-administration of a strong or moderate inhibitor is required because there is no suitable alternative medication, exception to this criterion may be allowed with a suitable dose reduction of olaparib (see section 5.5.2.1)

Strong or Moderate CYP3A inducers

Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib.

P-gp inhibitors

It is possible that co-administration of P-gp inhibitors (eg amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

Effect of olaparib on other drugs

Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

Based on limited in vitro data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp.

Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP1A2 – duloxetine, melatonin
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 -furosemide, methotrexate

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. Subcutaneous heparin and low molecular weight heparin are permitted.

Anti-emetics/Anti-diarrhoeals

If a patient develops nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs (see section XX) and appropriate treatment of the event given.

Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment.

Subsequent therapies for cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the exploratory assessments of survival.

5.9.1 Prohibited before enrollment and during administration of study treatment
Medications that are prohibited during study treatment and in the prior 6 months prior to enrollments: LHRH agonist / antagonist therapy, androgen receptor antagonists, and androgen synthesis inhibitors. 5-alpha reductase inhibitors are allowed if subject has been taking stable dose of medication for prior 6 months. Strong or moderate CYP3A inhibitors or inducers are prohibited during administration of study treatment; if a patient requires treatment with such a medication, then the

It is not recommended to consume grapefruit juice while on olaparib therapy. Patients should not consume grapefruit or Seville oranges while on treatment for olaparib.

5.10 Contraception
Patients with partners of child bearing potential, who are sexually active, must agree to the use of two highly effective forms of contraception throughout period of taking study treatment and for 3 months after last dose of study drug.

For details refer to Appendix E Acceptable Birth Control Methods.

6. THERAPEUTIC AGENT

6.1 Description of Treatments
The drug to be tested in this clinical protocol is olaparib (IND #). Olaparib will be supplied by AstraZeneca.

6.2 Pharmacokinetics
Olaparib is orally bioavailable with peak plasma concentrations occurring 1-3 hours after dosing. Steady state is achieved in 3-4 days. There are no requirements for consumption with food.

Olaparib is metabolized in the liver by CYP3A4, and is excreted in urine and feces. Mild renal impairment (CrCl 50-80) resulted in 1.2-1.5 increase in AUC for the drug, and the drug has not been studied in patients with CrCl < 50. No dosing reductions based upon CrCl are recommended.

6.3 Dosage Selected, Preparation, and Schedule of Administration

Olaparib will be dosed based upon guidelines in Section 5. Treatment will be administered on an outpatient basis. Olaparib is dosed twice daily. Patients will be asked to keep a drug diary and present bottles for assessment at each assessment.

6.3.1 Supply, storage requirements, and special handling

6.3.1.1 Supply and packaging

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply olaparib to the investigator as round or oval *film coated tablets*

Investigational product	Dosage form and strength
Olaparib	*150 mg tablet*
Olaparib	*100 mg tablet*

[a] Descriptive information for olaparib can be found in the Investigator's Brochure

6.3.1.2 Storage requirements

Store olaparib below 30deg C (Room temperature). Excursions above the recommended storage conditions should not exceed an upper temperature of 50deg C and a period of more than 7 days. After a temperature excursion the product should be returned immediately to the recommended storage conditions.

6.3.1.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. Label text will be translated into local language.

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

The label will include the following information:

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

6.4 Removing Patients from the Protocol

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment

- Severe non-compliance with the study protocol
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)
- Potential Hy's Law cases (AST or ALT ≥3x ULN and TBL ≥2xULN with no other reason)
- Disease progression by symptomatic or radiographic assessment
- PSA doubling from baseline value, confirmed by a second value at least 4 weeks apart, with a minimum time since initiation of therapy of 12 weeks.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the patient to be retreated.
- Adverse events requiring cessation of olaparib, with inability to restart therapy within 14 days.
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator

  Because an excessive rate of withdrawals can render the study uninterpretable, unnecessary withdrawal of patients should be avoided. When a patient discontinues treatment early, the investigator should make every effort to contact the patient and to perform a final evaluation. The reasons for withdrawal should be recorded.

6.5 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 bid (tablet).

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

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

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives

within one day, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 7.4. For other overdoses, reporting should be done within 30 days.

7. ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

7.1.2 Serious Adverse Event (SAE)

The investigator must assess each event to determine if it meets the criteria for classification as an SAE or serious adverse drug reaction.

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs 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 intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

7.1.3 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. An AESI may be serious or non-serious. Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

ANY event of MDS/AML, new primary malignancy, or pneumonitis should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE [eg non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm.

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

The development of a new primary cancer (including skin cancer) should be regarded as an AE. 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.

7.1.4 Progression of malignancy

Progression of a patient's malignancy should not be considered an AE, unless in the investigator's opinion, study treatment resulted in an exacerbation of the patient's condition. If disease progression results in death or hospitalization while on study or within 30 days of the last dose of olaparib, progressive disease will be considered an SAE.

7.1.5 Life-threatening events

A life-threatening event is any AE that places the patient at immediate risk of death from the reaction as it occurs. It is not a reaction that, had it occurred in a more severe form, might have caused death.

7.1.6 Hospitalization or prolongation of hospitalization

Hospitalization encompasses any inpatient admission (even for less than 24 hours) resulting from a precipitating, treatment-emergent adverse event. For chronic or long-term patients, inpatient admission also includes transfer within the hospital to an acute or intensive care inpatient unit. Hospitalizations for administrative reasons or a nonworsening preexisting condition should not be considered AEs (eg, admission for workup of a persistent pretreatment laboratory abnormality, yearly physical exam, protocol-specified admission, elective surgery). Preplanned treatments or surgical procedures should be noted in the baseline documentation. Hospitalization because of an unplanned event will be deemed an SAE.

Prolongation of hospitalization is any extension of an inpatient hospitalization beyond the stay anticipated or required for the original reason for admission.

7.1.7 Significant disability

Disability is a substantial disruption of the patient's ability to conduct normal life functions.

7.1.8 Pregnancy

Male participants 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) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 3 months *after the last dose* should be followed up and documented.

All outcomes of pregnancy should be reported to AstraZeneca.

7.1.9 Medical significance

An event that is not fatal or life-threatening and that does not necessitate hospitalization may be considered serious if, in the opinion of the investigator, it jeopardizes the patient's status and might lead to medical or surgical intervention to prevent any of the above outcomes. Such medically significant events could include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

7.1.10 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 eCRF 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 **Error! Reference source not found.** for further d etails). 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 the 'death eCRF'.

Deaths with an unknown cause should always be reported as a SAE. A post mortem 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.

The NCI CTCAE handbook v4.0 will be used for adverse event descriptions and grading.

Follow-up of adverse events should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator and the medical monitor (Dr. Catherine Handy Marshall).

Events that are **not** considered serious adverse events include:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

7.2 Expectedness

Adverse events can be considered, "expected," or, "unexpected."

7.2.1 Expected Adverse Events

Expected adverse events are those that have been previously identified as resulting from administration of the agent. An adverse event can be considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

7.2.2 Unexpected Adverse Events

An adverse event can be considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk. Contact the lead site, principal Investigator or sponsor to confirm unexpected adverse events when necessary.

7.3 Recording and Grading

7.3.1 Recording

All observed or volunteered adverse events, regardless of treatment group, severity, suspected causal relationship, expectedness, or seriousness will be documented.

A clinically significant change in a physical examination finding or an abnormal test result (ie, laboratory, x-ray, EKG) should be recorded as an AE, if it:

- is associated with accompanying symptoms
- requires additional diagnostic testing or medical or surgical intervention
- leads to a change in study dosing or discontinuation from the study

- requires additional concomitant drug treatment or other therapy, or
- is considered clinically significant by the investigator or sponsor

An abnormal test result that is subsequently determined to be in error does not require recording as an adverse event, even if it originally met one or more of the above criteria.

7.3.2 Grading severity

All adverse events will be graded for intensity on a scale of 0 to 5. Severity grades will be recorded and based on the most recent version of the NCI CTCAE handbook.

7.3.3 Attributing causality

After grading for severity, the investigator must evaluate all clinical AEs and abnormal laboratory values for possible causal relationship to olaparib. Causality attribution will be decided using the criteria outlined in Table 6.

Table 8 Relationship of Adverse Event to Study Drug

Relationship	Description
Unrelated	AE is clearly not related to Olaparib
Unlikely	AE is doubtfully related to Olaparib
Possible	AE may be related to Olaparib
Probable	AE is likely related to Olaparib
Definite	AE is clearly related to Olaparib

7.4 Reporting Adverse Events

7.4.1 Reporting serious adverse events

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

***** A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

External Scientific Research (ESR)

The investigator IND number assigned by the FDA

The investigator's name and address

The trial name/title and AstraZeneca ESR reference number

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

**** Send SAE report and accompanying cover page by way of Email to*** AEMailboxClinicalTrialTCS@astrazeneca.com ***or by fax to AstraZeneca's designated fax line:*** 302-886-4114

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

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the *30 day follow-up* period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for *30 calendar days after the last dose of trial drug and/or until event resolution.* All new AEs occurring during that period must be recorded (if SAEs, then they must be reported to the FDA and AstraZeneca). All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

7.4.3 Adverse events after the 30 day follow up period

For Pharmacovigilance purposes and characterisation, any case of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE [eg non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

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 the post treatment follow up period (30 days).

7.4.2 Reporting SAEs at multi-site/participating institutions
SAEs should be reported to the lead site and study sponsor.

7.5 Adverse Events Related to Olaparib

AE reports considered to be associated with administration of olaparib are generally mild or moderate (CTCAE Grade 1 or 2):

- haematological effects (anaemia, neutropenia, lymphopenia, thrombocytopenia, MCV elevation)
- decreased appetite
- nausea and vomiting
- diarrhea
- dyspepsia
- stomatitis
- upper abdominal pain
- dysgeusia, fatigue (including asthenia)
- increase in blood creatinine
- headache and dizziness
- rash

In a small number of patients, pneumonitis, MDS/AML and new primary malignancies have been reported, however totality of data from the whole development programme does not support a conclusion that there is a causal relationship between olaparib and these events.

8. CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE

8.1 Outcome Assessment

All baseline evaluations will be performed as closely as possible to the beginning of treatment (within 7 days). For subsequent evaluations, the method of assessment and techniques will be the same as those used at baseline.

- Tumor markers

  PSA measurements will be used to assess the primary endpoint.

8.1.1 Primary endpoint
The primary endpoint is defined as a PSA_{50} response, defined as a decline in PSA to 50% of baseline level, confirmed with a second measurement at least 4 weeks apart.

8.1.2 Secondary endpoints

8.1.2.1. Safety: this endpoint is defined as incidence of grade 3-5 toxicities based upon CTC v4.0 standard grading scales.

8.1.2.2. PSA Progression-Free Survival (PFS): PSA PFS is a time to event endpoint defined as from initiation of olaparib therapy until an increase in PSA of 25% over a nadir value, confirmed with a second measurement at least 4 weeks apart. The date of PSA progression will be the first value recorded (not the confirmatory value).

8.1.2.3. Time to PSA doubling from baseline: this endpoint is a time-to-event defined as time from initation of olaparib therapy until the PSA has increased to 200% of baseline value, confirmed with another measurement at least 4 weeks later. The date of PSA doubling will be the first value recorded (not the confirmatory value).

8.1.2.4. Undetectable PSA: This endpoint represents a durable complete response to therapy. It is defined as a PSA of <0.1 confirmed with a repeat measurement at least 12 weeks later.

8.2 Therapeutic Response

Response and progression will be evaluated in this study using guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG3). Because the population under study in this protocol has only a biochemical manifestation of disease, response is primarily evaluated based upon changes in PSA.

9. DATA REPORTING AND REGULATORY REQUIREMENTS

Multicenter Guidelines

The Protocol Chair

The Protocol Chair, Dr. Catherine Handy Marshall, is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the protocol
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)
- Reviewing data from all sites

Lead Center

The Lead Center (Johns Hopkins) is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.

- Managing central patient registration

- Collecting and compiling data from each site

- Establishing procedures for documentation, reporting and submitting of AE's and SAE's to the Protocol Chair and all other applicable parties.

- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating PCCTC Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).

- Submitting data to the Lead Center

- Registering all patients with the Lead Center by submitting patient registration form, and signed informed consent promptly

- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol

- Maintaining regulatory binders on site and providing copies of all required documents to the Lead Center

- Collecting and submitting data according to the schedule specified by the protocol

9.1 Data Entry

Data collected during this study will be entered into a secure database. Staff at the PCCTC coordinating center at MSKCC will be responsible for the initial study configuration and setup in the consortium database and for any future changes.

9.1.1 Case report forms

Case report forms will be generated by the coordinating center at MSKCC for the collection of all study data. Investigators will be responsible for ensuring that the CRFs are kept up-to-date.

9.1.2 Source documents

Study personnel will record clinical data in each patient's source documents (ie, the patient's medical record). Source documentation will be made available to support

the patient research record. Study monitors will review entries on the CRFs at regular intervals, comparing the content with source documents.

9.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents, study-related documents, and the CRFs. Because the length of time required for retaining records depends upon a number of regulatory and legal factors, documents should be stored until the investigator is notified that the documents may be destroyed. In this study, records are to be retained and securely stored for a minimum of 5 years after the completion of all study activities.

9.2 Data Management

9.2.1 Lead research program coordinators

A Lead research program coordinator at the coordinating center will be assigned to the study. A Lead Research Program Coordinator will manage the study activities at each of the participating sites. The responsibilities of the Lead Research Program Coordinator include project compliance, data collection, data entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol team.

9.3 Study Monitoring and Quality Assurance

Regularly scheduled registration reports will be generated to monitor patient accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the principal investigator for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team at least once a year, more frequently if indicated. Audits by the coordinating center may entail (1) shipping source documents and research records for selected patients from participating sites to the coordinating center for audit, or (2) on-site auditing of selected patient records at participating sites.

All clinical work conducted under this protocol is subject to Good Clinical Practice (GCP) guidelines. This includes inspection of study-related records by the lead site, sponsor, its designee, or health authority representatives at any time.

9.4 Clinical Trial Agreement

This trial is being conducted under one or more clinical trial agreements that contain, among other terms, the publication policy, indemnity agreements, and financial arrangements for the study.

9.5 SKCCC Data and Safety Monitoring Plan

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU

affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

10. STATISTICAL CONSIDERATIONS

This study will enroll up to 50 subjects. The study design will employ a stepwise adaptive statistical plan, derived in part from Biankin *et al.* [27]. The design is adapted from a multi-stage design, with interim stopping rules to determine futility or need for enrichment of the study population.

The study will initiate with a two-stage design in an unselected population. The assumptions for the trial of the unselected population are: null hypothesis of 0.1 PSA response rate and alternative hypothesis of 0.3 for the unselected population. The first stage is 20 subjects. If ≤2 subjects responds in the first stage, then unselected population study is halted for futility and an assessment of DNA mutations present in the initial cohort will be undertaken. If less than 3 subjects with a known/suspected deleterious mutation in the following genes (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or other DNA repair genes) have been accrued in the first stage, then the trial will proceed with enrichment. If 3 or more subjects with known/suspected deleterious mutation in the genes of interest have been accrued, then the trial will proceed with enrichment, as long as the response rate in that subset of subjects is ≥20%. In the case that 3 or more subjects have been accrued, yet the response rate in that subset is <20%, then the trial is halted for futility.

However, if ≥3 subjects among the first 20 respond, then additional 10 unselected subjects are accrued. If ≥6 subjects respond out of 30 in the unselected population after the second stage, then the null hypothesis is rejected in the unselected population and broad efficacy will be concluded. The trial proceeds to complete accrual of 50 subjects in order to better estimate PSA response rate and strengthen data for correlative studies. If <6 respond, then the null hypothesis is not rejected. Again, if less than 3 subjects with a known/suspected deleterious mutation in the following genes (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or other DNA repair genes) have been accrued in the first and second stage combined, then the trial will proceed with enrichment. If 3 or more subjects with those mutations have been accrued, then enrichment will again proceed as long as the response rate in that subject of subjects is ≥20%.

An enriched population will be required to have a known/suspected deleterious mutation in of the genes listed above. The data for the enriched population will be analyzed separately from the data in the first (and second, if applicable) stage(s). The assumptions for the enriched population: null hypothesis of 0.3 PSA response rate, and alternative hypothesis of 0.6 for the biomarker selected population. The sample size for the selected population is 20 subjects. If ≥10 respond, the null is rejected for the biomarker selected population and efficacy will be concluded for the biomarker subgroup.

This design will have power for detecting an effect in the unselected population of 0.90-0.91 and a power for detecting an effect in the selected population (if there is no effect in the

unselected) of 0.79-0.80, with an overall type I error 0.1-0.11, assuming the biomarker prevalence 10-15%, based upon 10,000 simulations of possible outcomes.

10.1 Study Endpoints

10.1.1 Analysis of the primary endpoint

The primary endpoint of this study is PSA_{50} response, defined as a decrease in the PSA to 50% less than the baseline PSA upon enrollment in the trial. The decrease must be confirmed by a second measurement at least 4 weeks apart. For purposes of meeting the primary endpoint, patients will be considered to have done so if they have a PSA_{50} response only while on therapy with olaparib. The confirmatory value may be drawn off therapy for olaparib. PSA values will be measured each cycle during the trial. All patients who are administered at least one dose of olaparib will be considered evaluable for the primary endpoint. If patients do not have follow-up PSAs after initiation olaparib therapy due to stopping therapy for toxicity or withdrawing consent, for example, then they will be considered non-responders. If the biomarker-enriched stage is necessary, that cohort will be evaluated separately from the initial stage(s) of the trial.

We will estimate the PSA_{50} response rate, along with the exact 95% confidence interval, for the population of patients. If a biomarker-selected population is accrued, it will be analyzed separately from the previously accrued unselected population.

10.1.2 Analysis of secondary endpoints

10.1.2.1. Safety

Patients will be assessed for toxicities at each clinical evaluation. Toxicities will graded according to CTC v4.0 standardized grading scales. The incidence of grade 3-5 toxicities will be reported. Patients will be assessed for toxicity as long as they are taking olaparib, and patients will continue to be followed if olaparib is discontinued for toxicity until the toxicities improve to grade 1 or resolve

Toxicities will be reported as a tabulated table by type and grade.

If >1 participant is diagnosed with MDS or AML during the trial, then the trial will be stopped for concerns about safety.

10.1.2.2. PSA progression-free survival (PFS)

Patients in this trial can remain on olaparib as long as they are not experiencing toxicity requiring cessation of drug and until their PSA reaches a value that is double that of the value on enrollment in the study. However, for purposes of reporting this secondary endpoint, a standard definition of PSA progression per PCWG3 will be used. PSA PFS will be defined as an increase in 25% over a nadir value, confirmed by a follow-up PSA at least 4 weeks apart. If patients are removed from study prior to PSA progression, then they will be censored at that time.

We will use the Kaplan-Meier method to estimate the median PSA PFS.

10.1.2.3. Time to PSA doubling from baseline:
Patients in this trial can remain on olaparib as long as they are not experiencing toxicity requiring cessation of drug, not experiencing clinical progression of disease, and until their PSA reaches a value that is double that of the value on enrollment in the study. A confirmatory PSA at least 4 weeks later is required; and the time point used for calculation of this endpoint will be the first of those values.

We will use the Kaplan-Meier method to estimate the median time to PSA doubling.

10.1.2.4. Undetectable PSA:
A durable undetectable PSA endpoint will be defined as a patient on study with olaparib who achieves a PSA < 0.1, which is confirmed with a repeat measurement at least 12 weeks later. This endpoint will represent a durable complete metabolic response to olaparib. This endpoint can only be achieved while on therapy with olaparib, although the confirmatory values after initially achieving undetectable PSA may be measured while off therapy for olaparib.

The durable complete PSA response rate will be estimated as number of patients achieving a durable complete PSA response divided by enrolled patients with an exact 95% confidence interval.

10.1.2 Analysis of exploratory endpoints

10.1.2.1. Biomarker positive and biomarker negative PSA_{50} response calculations: All subjects in the trial will be considered either a responder or non-responder based upon the meeting of the primary endpoint based upon the definition above. For each patient, the DNA mutations present in the tumor will be identified through Foundation Medicine sequencing and/or through plasma cell-free DNA analysis. Patients with a deleterious mutation in the pre-specified gene list (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or other DNA repair genes) will be considered biomarker positive. For biomarker positive and biomarker negative subjects, we will calculate response rates with confidence intervals for hypothesis generation. Separate calculations for each testing modality will occur. If a biomarker selected population is accrued, then the response rate in the biomarker positive population will be reported as the primary analysis. If the trial proceeds with an unselected population only, then these calculations will be reported as exploratory endpoints.

10.1.2.2. Development of gene signature for response: based upon the responders and the DNA mutations identified through sequencing, a discovery of a biomarker set will take place by exploring which grouping of mutations are associated with response, using both descriptive analyses and random forest methods.

10.1.2.3. RNA expression profile signature positive and negative PSA_{50} response calculations: Similarly to above, subjects will have tumor tested with RNA expression profiling and scored for likelihood for response to olaparib per the Decipher GRID platform (GenomeDx). For subjects considered to have a positive

RNA expression signature based upon a binary score assigned via the GenomeDx proprietary algorithm, a PSA_{50} response rate will be calculated. Similarly, a calculation will be performed for subjects considered to have a negative RNA expression signature.

10.1.2.4. PARP-1 and γH2AX protein levels: Subjects will have prostatectomy samples analyzed for baseline PARP-1 and γH2AX proteins, and scored for positivity by immunohistochemistry on scale of 0 (none) to 3 (intense staining), and the results will be associated with responses for both proteins, separately, using descriptive statistics and Fisher's Exact Tests.

10.1.2.5. Metastasis-free survival analysis: the median MFS will be estimated using the Kaplan-Meier method.

10.1.2.6. Time to next anti-cancer therapy analysis: similarly to MFS, this time to event analysis will be estimated using the Kaplan-Meier method.

10.2 Operating Characteristics of Clinical Trial Design

The operating characteristics of the multi-stage adaptive design were illustrated in a 10,000-iteration simulation. The simulations employed the assumptions outlined above (unselected population study: alpha 0.10, power 0.90, H0 = 0.1, H1 = 0.3; selected population study: alpha 0.10, power 0.80, H0 = 0.3, H1 = 0.6) in a 50 subject study.

10.2.1 *Estimation of Type 1 Error*
Assuming that the response rates for all-comers is 0.1 and the response rate for the biomarker selected population is 0.3 (both null hypotheses), estimates for type 1 error were generated using the simulation. Two scenarios are presented: prevalence of biomarker positive subjects of 10% and 15% in the population.

Scenario	N Stage 1	N Stage 2	N Enriched	N Total	≥N to Reject Stage 1	≥N to Reject Stage 2	Type 1 Error All-comers	Type 1 Error Biomarker+	Type 1 Error Combined
10% Biomarker +	20	10	20	50	3	6	0.07	0.04	0.11
15% Biomarker +	20	10	20	50	3	6	0.07	0.03	0.10

The proportion of trials that are stopped for futility in this simulation, with or without enrichment, is presented below:

Scenario	Stage 1 Futility No Enrichment	Stage 2 Futility No Enrichment	Enrichment Futility

10% Biomarker +	0.09	0.03	0.78
15% Biomarker +	0.15	0.03	0.72

10.2.2 *Estimation of Power*
Assuming that the response rates for all-comers is 0.3 and the response rate for the biomarker selected population is 0.6 (both alternative hypotheses), estimates for power were generated using the simulation. Two scenarios are presented: prevalence of biomarker positive subjects of 10% and 15% in the population.

Scenario	N Stage 1	N Stage 2	N Enriched	N Total	≥N to Reject Stage 1	≥N to Reject Stage 2	Power All-comers	Power Biomarker+	Power Combined
10% Biomarker +	20	10	20	50	3	6	0.92	0.07	0.98
15% Biomarker +	20	10	20	50	3	6	0.91	0.07	0.98

The proportion of trials that are stopped for futility in this simulation, with or without enrichment, is presented below:

Scenario	Stage 1 Futility No Enrichment	Stage 2 Futility No Enrichment	Enrichment Futility
10% Biomarker +	0.00	0.00	0.01
15% Biomarker +	0.00	0.01	0.01

10.2.3 *Estimation of Power (in case enrichment is needed to demonstrate efficacy)*
Assuming that the response rates for all-comers is 0.1 and the response rate for the biomarker selected population is 0.6 (null in all-comer, alternative in selected), estimates for power were generated using the simulation. Two scenarios are presented: prevalence of biomarker positive subjects of 10% and 15% in the population.

Scenario	N Stage 1	N Stage 2	N Enriched	N Total	≥N to Reject Stage 1	≥N to Reject Stage 2	Power All-comers	Power Biomarker+	Power Combined

10% Biomarker +	20	10	20	50	3	6	0.07	0.80	0.87
15% Biomarker +	20	10	20	50	3	6	0.07	0.79	0.86

The proportion of trials that are stopped for futility in this simulation, with or without enrichment, is presented below:

Scenario	Stage 1 Futility No Enrichment	Stage 2 Futility No Enrichment	Enrichment Futility
10% Biomarker +	0.02	0.00	0.12
15% Biomarker +	0.02	0.00	0.12

10.2.3 *Estimation of Power with variable assumptions of response rates for subpopulations*
The probably of response in the all-comer population is varied from 0.05 to 0.30 and 0.20-0.60 in the biomarker-selected population.

Scenario #	Resp. Rate Biomarker-	Resp. Rate Biomarker+	Resp. Rate All-comer	Proportion Biomarker+	Power All-comers	Power Biomarker+	Power Combined
1	0.03	0.20.20	0.05 0.05	0.10 0.10	0.00 0.00	0.00 0.00	0.00
2	0.09	0.20.20	0.10 0.10	0.10 0.10	0.07 0.07	0.07 0.07	0.07
3	0.14	0.20.20	0.15 0.15	0.10 0.10	0.27 0.27	0.27 0.27	0.27
4	0.20	0.20.20	0.20 0.20	0.10 0.10	0.55 0.55	0.55 0.55	0.55
5	0.26	0.20.20	0.25 0.25	0.10 0.10	0.78 0.78	0.78 0.78	0.78
6	0.31	0.20.20	0.30 0.30	0.10 0.10	0.91 0.91	0.91 0.91	0.91
7	0.02	0.30.30	0.05 0.05	0.10 0.10	0.00 0.00	0.04 0.04	0.05
8	0.08	0.30.30	0.10 0.10	0.10 0.10	0.07 0.07	0.14 0.14	0.11
9	0.13	0.30.30	0.15 0.15	0.10 0.10	0.27 0.27	0.33 0.33	0.30
10	0.19	0.30.30	0.20 0.20	0.10 0.10	0.55 0.55	0.56 0.56	0.56
11	0.24	0.30.30	0.25 0.25	0.10 0.10	0.78 0.78	0.79 0.79	0.79
12	0.30	0.30.30	0.30 0.30	0.10 0.10	0.91 0.91	0.91 0.91	0.91
13	0.01	0.40.40	0.05 0.05	0.10 0.10	0.00 0.00	0.23 0.23	0.23
14	0.07	0.40.40	0.10 0.10	0.10 0.10	0.07 0.07	0.28 0.28	0.28
15	0.12	0.40.40	0.15 0.15	0.10 0.10	0.27 0.27	0.43 0.43	0.43
16	0.18	0.40.40	0.20 0.20	0.10 0.10	0.54 0.54	0.64 0.64	0.64
17	0.23	0.40.40	0.25 0.25	0.10 0.10	0.78 0.78	0.82 0.82	0.82
18	0.29	0.40.40	0.30 0.30	0.10 0.10	0.91 0.91	0.93 0.93	0.93

19	0.00	0.50	0.50	0.05	0.05	0.10	0.10	0.00	0.06	0.57
20	0.06	0.50	0.50	0.10	0.10	0.10	0.10	0.07	0.52	0.59
21	0.11	0.50	0.50	0.15	0.15	0.10	0.10	0.27	0.41	0.68
22	0.17	0.50	0.50	0.20	0.20	0.10	0.10	0.55	0.25	0.80
23	0.22	0.50	0.50	0.25	0.25	0.10	0.10	0.78	0.12	0.90
24	0.28	0.50	0.50	0.30	0.30	0.10	0.10	0.91	0.04	0.96
25	0.04	0.60	0.60	0.10	0.10	0.10	0.10	0.07	0.80	0.87
26	0.10	0.60	0.60	0.15	0.15	0.10	0.10	0.28	0.62	0.90
27	0.16	0.60	0.60	0.20	0.20	0.10	0.10	0.54	0.39	0.93
28	0.21	0.60	0.60	0.25	0.25	0.10	0.10	0.78	0.18	0.96
29	0.27	0.60	0.60	0.30	0.30	0.10	0.10	0.91	0.08	0.98
30	0.02	0.20	0.20	0.05	0.05	0.15	0.15	0.00	0.00	0.00
31	0.08	0.20	0.20	0.10	0.10	0.15	0.15	0.07	0.00	0.07
32	0.14	0.20	0.20	0.15	0.15	0.15	0.15	0.27	0.00	0.27
33	0.20	0.20	0.20	0.20	0.20	0.15	0.15	0.55	0.00	0.55
34	0.26	0.20	0.20	0.25	0.25	0.15	0.15	0.78	0.00	0.78
35	0.32	0.20	0.20	0.30	0.30	0.15	0.15	0.91	0.00	0.91
36	0.01	0.30	0.30	0.05	0.05	0.15	0.15	0.00	0.04	0.04
37	0.06	0.30	0.30	0.10	0.10	0.15	0.15	0.07	0.04	0.10
38	0.12	0.30	0.30	0.15	0.15	0.15	0.15	0.28	0.03	0.30
39	0.18	0.30	0.30	0.20	0.20	0.15	0.15	0.55	0.01	0.56
40	0.24	0.30	0.30	0.25	0.25	0.15	0.15	0.78	0.01	0.78
41	0.30	0.30	0.30	0.30	0.30	0.15	0.15	0.91	0.00	0.91
42	0.05	0.40	0.40	0.10	0.10	0.15	0.15	0.07	0.20	0.27
43	0.11	0.40	0.40	0.15	0.15	0.15	0.15	0.27	0.15	0.42
44	0.16	0.40	0.40	0.20	0.20	0.15	0.15	0.55	0.09	0.64
45	0.22	0.40	0.40	0.25	0.25	0.15	0.15	0.77	0.04	0.81
46	0.28	0.40	0.40	0.30	0.30	0.15	0.15	0.91	0.01	0.92
47	0.03	0.50	0.50	0.10	0.10	0.15	0.15	0.07	0.52	0.59
48	0.09	0.50	0.50	0.15	0.15	0.15	0.15	0.28	0.39	0.67
49	0.15	0.50	0.50	0.20	0.20	0.15	0.15	0.55	0.24	0.79
50	0.21	0.50	0.50	0.25	0.25	0.15	0.15	0.78	0.11	0.89
51	0.26	0.50	0.50	0.30	0.30	0.15	0.15	0.91	0.04	0.95
52	0.01	0.60	0.60	0.10	0.10	0.15	0.15	0.07	0.79	0.86
53	0.07	0.60	0.60	0.15	0.15	0.15	0.15	0.28	0.61	0.89
54	0.13	0.60	0.60	0.20	0.20	0.15	0.15	0.55	0.38	0.93
55	0.19	0.60	0.60	0.25	0.25	0.15	0.15	0.78	0.18	0.96
56	0.25	0.60	0.60	0.30	0.30	0.15	0.15	0.91	0.07	0.98

The proportion of trials that are stopped for futility for these simulations, with or without enrichment, is presented below:

Scenario #	Stage 1 Futility No Enrichment	Stage 2 Futility No Enrichment	Enrichment Futility
1	0.15	0.01	0.84
2	0.12	0.05	0.76
3	0.08	0.08	0.56
4	0.05	0.08	0.32
5	0.03	0.05	0.15
6	0.01	0.02	0.05
7	0.10	0.00	0.85
8	0.08	0.03	0.78
9	0.06	0.05	0.59
10	0.04	0.05	0.35
11	0.02	0.03	0.16
12	0.01	0.02	0.06
13	0.06	0.00	0.71
14	0.05	0.01	0.65
15	0.04	0.03	0.50
16	0.02	0.03	0.30
17	0.01	0.02	0.14
18	0.01	0.01	0.06
19	0.03	0.00	0.40
20	0.03	0.00	0.38
21	0.02	0.01	0.28
22	0.01	0.02	0.17
23	0.01	0.01	0.08
24	0.00	0.01	0.03
25	0.01	0.00	0.11
26	0.01	0.00	0.09
27	0.01	0.01	0.05
28	0.00	0.01	0.02
29	0.00	0.00	0.01
30	0.28	0.01	0.71
31	0.23	0.07	0.62
32	0.16	0.13	0.43
33	0.09	0.12	0.24
34	0.05	0.07	0.10
35	0.02	0.04	0.03
36	0.18	0.00	0.78
37	0.16	0.03	0.71
38	0.11	0.08	0.51
39	0.07	0.08	0.29

40	0.03	0.05	0.13
41	0.02	0.03	0.05
42	0.09	0.01	0.63
43	0.07	0.04	0.47
44	0.05	0.04	0.27
45	0.03	0.03	0.13
46	0.01	0.02	0.05
47	0.05	0.00	0.36
48	0.04	0.01	0.28
49	0.03	0.02	0.16
50	0.02	0.02	0.08
51	0.01	0.01	0.03
52	0.02	0.00	0.11
53	0.02	0.00	0.09
54	0.01	0.01	0.05
55	0.01	0.01	0.02
56	0.01	0.01	0.01

10.3 Analysis Populations

10.3.1 Evaluable population

All patients who meet eligibility criteria and receive at least 1 dose of study medication will be included in the primary analysis of the response rate, even if there are major protocol deviations (eg, incorrect treatment schedule or drug administration). Each patient will be assigned to one of the following categories:

Conclusions are to be based on the population of all eligible patients. Supportive analysis and sensitivity analysis may be performed on various subsets of patients, such as those with no major protocol deviations or those who continued in the study for the entire treatment period (ie, did not withdraw prematurely). Subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy.

10.3.2 Safety population

All patients enrolled in the study will be included in the safety analysis population and considered evaluable for toxicity and safety from the time of their first dose. Demographic and baseline characteristics for the safety population will be summarized by number and percent for categorical data (eg, sex, race/ethnicity) and by descriptive statistics for continuous data (eg, weight, vital signs, EKG readings, disease status).

10.4 Safety Analysis

10.4.1 Evaluation of adverse events

Treatment-emergent adverse events will be translated from investigator terms to MedDRA v6.0 terminology and summarized (number and percentage of patients) for all patients who receive at least 1 dose. Adverse event summaries will be organized by body system, frequency of occurrence, intensity (ie, severity grade), and causality or attribution. Patients who experience an adverse event more than once will be counted only once. The occurrence with the maximum severity will be used to calculate intensity.

10.4.2 Evaluation of serious adverse events and premature withdrawals

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

10.4.3 Evaluation of laboratory parameters and assays

Selected clinical laboratory parameters will be summarized and clinically significant changes from baseline will be discussed.

10.4.4 Extent of exposure

Treatment exposure will be summarized for all patients, including dose administration, number of cycles, dose modifications or delays, and duration of therapy.

11. PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Considerations

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonisation, and the ethical standards set forth in the Declaration of Helsinki 2004 (available at: www.laakariliitto.fi/e/ethics/helsinki.html).

11.2 Protocol Amendments

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

11.3 Written Informed Consent

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

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

The consent form will include the following:

- the nature and objectives, potential toxicities, and benefits of the intended study
- the length of therapy and likely follow-up required
- alternatives to the proposed therapy (including available standard and investigational therapies)
- the name of the investigator(s) responsible for the protocol
- the right of the patient to accept or refuse treatment and to withdraw from participation in this study
- Text regarding the consortium and the coordinating center should be added to all institutional informed consent documents and sections in the research authorization/HIPAA forms (eg, "Prostate Cancer Clinical Trial Consortium, Coordinating Center at Memorial Sloan-Kettering Cancer Center, New York, NY")

11.4 Protection of Privacy

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

11.5 Terminating or Modifying the Study

Adverse event and laboratory data from this trial will be assessed by the medical monitor (Dr. Catherine Handy Marshall) on an ongoing basis. At least quarterly, data from the clinical database will be reviewed. The results of this review will be shared with all investigators either in writing or as part of a teleconference. SAEs will be reviewed as they are reported to the lead site/sponsor, and the medical monitor will make an assessment regarding the safety of continuing or modifying the study. This assessment will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the lead site/sponsor or the principal investigator be that the study should be terminated, the study will be closed to further accrual. Patients who are receiving olaparib will be assessed individually by the investigator to see if it is in the patients' best interest to continue, which might be the case for a patient that is responding to the intervention. Follow-up safety assessments will be performed for all patients who are terminated from the study prematurely.

12. REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: a cancer journal for clinicians. 2016;66(1):7-30.
2. 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):1402-18.
3. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: Recommendations from the prostate-specific antigen working group. J Clin Oncol. 1999;17(11):3461-7.
4. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol. 2007;25(15):2035-41.
5. Nguyen T, Boldt RG, Rodrigues G. Prognostic Factors for Prostate Cancer Endpoints Following Biochemical Failure: A Review of the Literature. Cureus. 2015;7(1):e238.
6. Antonarakis ES, Feng ZY, Trock BJ, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. Bju Int. 2012;109(1):32-9.
7. Suzman DL, Cullen J, Trock BJ, et al. PSA doubling time (PSADT) <=6 months to identify a subgroup of men with biochemically-recurrent prostate cancer (BRPC) after prostatectomy (RP) at highest risk of distant metastasis (dMET). ASCO Meeting Abstracts. 2016;34(15_suppl):e16587.
8. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917-21.
9. Hay T, Matthews JR, Pietzka L, et al. Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. Cancer research. 2009;69(9):3850-5.
10. Rottenberg S, Jaspers JE, Kersbergen A, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. P Natl Acad Sci USA. 2008;105(44):17079-84.
11. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. The New England journal of medicine. 2009;361(2):123-34.
12. Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: Clearing up the misunderstandings. Mol Oncol. 2011;5(4):387-93.
13. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer research. 2012;72(21):5588-99.
14. Kim G, Ison G, McKee AE, et al. FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy. Clinical cancer research : an official journal of the American Association for Cancer Research. 2015;21(19):4257-61.
15. Brenner JC, Ateeq B, Li Y, et al. Mechanistic rationale for inhibition of poly(ADP-ribose) polymerase in ETS gene fusion-positive prostate cancer. Cancer cell. 2011;19(5):664-78.
16. Gani C, Coackley C, Kumareswaran R, et al. In vivo studies of the PARP inhibitor, AZD-2281, in combination with fractionated radiotherapy: An exploration of the therapeutic ratio. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2015;116(3):486-94.

17. Tesson M, Rae C, Nixon C, et al. Preliminary evaluation of prostate-targeted radiotherapy using (131) I-MIP-1095 in combination with radiosensitising chemotherapeutic drugs. The Journal of pharmacy and pharmacology. 2016;68(7):912-21.
18. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33(3):244-50.
19. 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):1697-708.
20. Cancer Genome Atlas Research N. The Molecular Taxonomy of Primary Prostate Cancer. Cell. 2015;163(4):1011-25.
21. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015;161(5):1215-28.
22. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. The New England journal of medicine. 2016.
23. Paller CJ, Antonarakis ES. Management of biochemically recurrent prostate cancer after local therapy: evolving standards of care and new directions. Clinical advances in hematology & oncology : H&O. 2013;11(1):14-23.
24. Erho N, Crisan A, Vergara IA, et al. Discovery and Validation of a Prostate Cancer Genomic Classifier that Predicts Early Metastasis Following Radical Prostatectomy. Plos One. 2013;8(6).
25. Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a Genomic Classifier that Predicts Metastasis Following Radical Prostatectomy in an At Risk Patient Population. J Urology. 2013;190(6):2047-53.
26. Freedland SJ, Choeurng V, Howard L, et al. Utilization of a Genomic Classifier for Prediction of Metastasis Following Salvage Radiation Therapy after Radical Prostatectomy. European urology. 2016.
27. Biankin AV, Piantadosi S, Hollingsworth SJ. Patient-centric trials for therapeutic development in precision oncology. Nature. 2015;526(7573):361-70.

APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	**%**	**Description**
0	Normal activity. Fully active, able to continue all predisease performance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity, minor signs or symptoms of disease
1	Symptoms, but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair > 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled, cannot carry on any self-care, totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX B: MEDICATIONS WITH THE POTENTIAL FOR DRUG-DRUG INTERACTIONS

Class	Agents
Strong CYP3A inhibitors	e.g. itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritinovir, lopinavir/ritinovir, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir
Moderate CYP3A inhibitors	e.g. amprenavir, aprepitant, atazanavir, ciprofloxacin, daarunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil
Strong CYP3A Inducers	e.g. phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort

APPENDIX C: LABORATORY MANUAL

Pathology will be reviewed and processed centrally at Johns Hopkins. Radical prostatectomy specimens will be handled and sampled in a uniform fashion.
Upon enrollment in the clinical trial, tissue blocks from the prostatectomy will be sent to Johns Hopkins:

Tamara Lotan, M.D.
Department of Pathology
Johns Hopkins School of Medicine
CRB2 Room 343
1550 Orleans Street
Baltimore, MD 21231

The lead pathologist at Johns Hopkins, Dr. Tamara Lotan, will perform the central review and prepare tissue for correlative analysis.

- 10 unstained slides and 1 H&E slide representative of tumor will be prepared and send to Foundation Medicine for FoundationOne testing. Tumor will be placed in the FoundationOne specimen kit and mailed to:
  Foundation Medicine, Inc.
  7010 Kit Creek Road
  Morrisville, NC 27560
  Phone: 888.988.3639

- 10 unstained slides representative of tumor will be prepared and send to the Schiewer laboratory at Thomas Jefferson for PARP-1 and γH2AX Protein Analysis:
  Attn: Matt Schiewer, PhD
  Karen Knudsen Lab
  Kimmel Cancer Center
  Thomas Jefferson University
  233 S. 10th St
  BLSB 1008
  Philadelphia, PA 19107

- Two 1.5mm punch samples will be prepared and send to GenomeDx for RNA expression analysis. In the case that FFPE blocks are not available, 15 unstained slides will be employed to create the samples. Samples will be stored at 4deg C until placement in cooler shipping box with ice packs and mailed to:
  GenomeDx Biosciences Laboratory
  10355 Science Center Drive
  Suite 240
  San Diego, CA 92121

- 5 unstained slides representative of tumor will be prepared and banked, for those subjects consenting to optional tissue banking for future research

APPENDIX D: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ADR	adverse drug reaction
ADT	androgen-deprivation therapy
AE	adverse event
ANC	absolute neutrophil count
AUC	area under the plasma concentration-time curve
bid	bis in die (twice a day)
BMI	body mass index
BP	blood pressure
C	Celsius
CBC	complete blood count
Crcl	creatinine clearance
CRF	case report form
CRMIS	Clinical Research Management Information System
CRPC	castration resistant prostate cancer
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome p-450
dL	deciliter
ECOG	Eastern Cooperative Oncology Group
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
IND	investigational new drug
IRB	Institutional Review Board
PFS	progression-free survival
PI	principal investigator
PO	per os (by mouth)
PSA	prostate-specific antigen
PSA-DT	prostate-specific antigen doubling time

APPENDIX E. ACCEPTABLE BIRTH CONTROL METHODS

Olaparib is regarded as a compound with medium/high fetal risk. Subjects with partners of childbearing potential, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

Acceptable Non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must continue for the total duration of study treatment and for at least 1 month after the last dose. Periodic abstinence (eg, calendar ovulation, symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- 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 F. ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN – HY'S LAW

1. INTRODUCTION

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

2. DEFINITIONS

Potential Hy's Law (PHL)

- Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP).
- The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

- AST or ALT ≥ 3x ULN and TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.
- The elevations do not have to occur at the same time or within aspecified time frame.

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 ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

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

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

4. FOLLOW-UP

Potential Hy's Law Criteria not met
If the patient does not meet PHL criteria the Investigator will:

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

Potential Hy's Law Criteria met
If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:
- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

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. No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate. According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

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

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

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. 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 chronic or progressing malignant disease?

  - If No: follow the process described in Section 4 of this Appendix

  - If Yes: Determine if there has been a significant change in the patient's condition# compared with when PHL criteria were previously met
    - If there is no significant change no action is required
    - If there is a significant change follow the process described in Section 4 of this Appendix

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

7. REFERENCES

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