Phase II Study of PARP Inhibitor Olaparib and IV Ascorbate in Metastatic Castration Resistant Prostate Cancer

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INVESTIGATOR'S APPROVAL OF PROTOCOL

Title: **Phase II Study of PARP Inhibitor Olaparib and IV Ascorbate in Metastatic Castration Resistant Prostate Cancer**

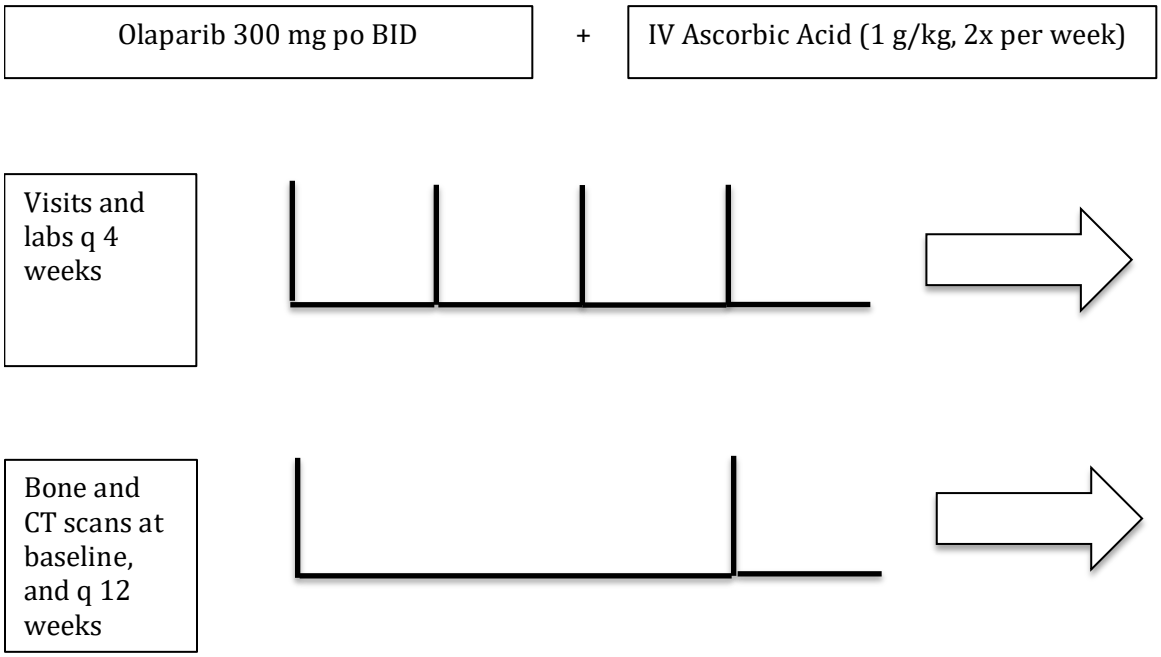
Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

1.0 SCHEMA

Total Number of Patients: 15



Olaparib is taken 300 mg BID orally

Ascorbate is given 1 g/kg, 2 times per week intravenously (first three doses [over 1.5 weeks]: titrate 0.25 g/kg, 0.5 g/kg, and 0.75 g/kg. Starting with cycle 1 week 2, the dose of Ascorbate will be 1 g/kg as long as this dose is tolerated)

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2.0 OBJECTIVES

2.1 Primary Objective

To estimate the proportion of patients with metastatic castration resistant prostate cancer (mCRPC) having a 50% reduction in PSA from baseline (PSA50 response).

2.2 Secondary Objectives

1) To evaluate the safety and tolerability of olaparib in combination with IV ascorbic acid in patients with mCRPC.

2) To estimate the median time to PSA doubling from baseline of patients with mCRPC receiving olaparib in combination with IV ascorbic acid.
3) To estimate the median radiographic progression free survival (rPFS) of patients with mCRPC receiving olaparib in combination with IV ascorbic acid.
4) To estimate the median PSA progression free survival (PSA PFS) of patients with mCRPC receiving olaparib in combination with IV ascorbic acid.
5) To assess overall survival (OS) in patients with castration resistant prostate cancer.

2.3 Exploratory Objectives

Examine correlates that may be predictive of PSA_{50} response and rPFS.

1) To quantify ctDNA and perform mutational analysis in the peripheral blood and compare it to any baseline germline or somatic mutations (document prestudy on case report form).
2) To quantify circulating tumor cells (CTCs) in the peripheral blood at baseline, 4 weeks, 12 weeks, and upon progression and assess γH2AX foci in CTCs.
3) Optional γH2AX foci FFPE biopsy tissues.
4) To measure F2-isoprostanes in the urine as a pharmacodynamic measure of oxidant injury at baseline, 4 weeks, 12 weeks, and upon progression.
5) To measure 8-oxo-2'-deoxyguanosine as a measure of oxidative stress in the urine at baseline, 4 weeks, 12 weeks, and upon progression.

3.0 STUDY DESIGN

This is a multi-center phase II study to evaluate the safety and clinical activity of the combination of olaparib and high-dose IV ascorbate, as second or later line of therapy, in castration resistant prostate cancer patients with no known DNA repair gene mutations (DDRm). In brief, the primary endpoint is PSA_{50} response, defined by a 50% reduction in PSA from baseline. The secondary endpoints are assessing the PSA doubling time, radiographic and PSA PFS, safety and tolerability as defined by the incidence of grade 3 to 5 toxicities, and measuring overall survival. For complete endpoint definitions, see **Sections 13.2-13.4**. The total accrual for this clinical trial will be 12 men with castration resistant prostate cancer (n=12).

Olaparib will be administered at 300 mg PO BID; ascorbate will be administered at 1 g/kg IV twice weekly at least 24 hours apart until objective disease progression or unacceptable toxicities or patient withdrawal for other reasons.

The study will consist of a screening period (within 28 days of the first dose), treatment period, and follow-up period. Dose reductions are allowed per **Section 8.2.** Enrollment will continue until 15 subjects (allows for 3 drop outs) have received at least one dose of study treatment.

4.0 BACKGROUND

4.1 Disease Background

Prostate cancer (PC) is the most commonly diagnosed malignancy and the second leading cause of cancer death in men. Radical prostatectomy and radiation therapy are the established definitive treatments for clinically localized PC; yet, 50,000 men each year progress with a biochemical relapse while others develop metastatic disease resulting in over 30,000 deaths annually. While chemical castration is temporarily effective in many patients, most men eventually progress to castrate-resistant prostate cancer (CRPC) and are then treated with docetaxel-based chemotherapy.

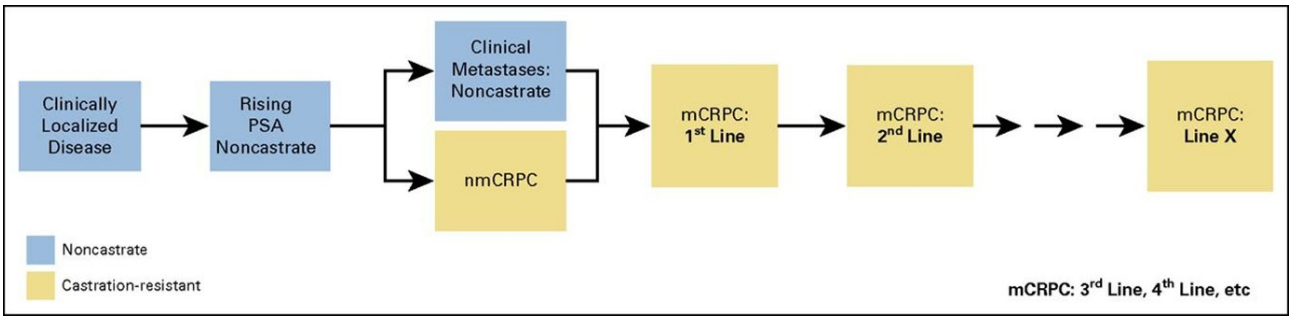

Figure 1: Clinical states of prostate cancer[1]

4.2 Treatment Background

4.2.1 Description and mechanism of action of Olaparib

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.[2] 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. Olaparib [Lynparza] was approved by the FDA for treatment of men with prostate cancer who have deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated metastatic castration resistant prostate cancer who have progressed on Abiraterone or Enzalutamide.

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[3,4] and in the clinic.[5] The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair.[6,7] Persistence of SSBs during DNA replication results in their conversion into the more serious 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 stand-alone treatment or in combination with established chemotherapies.

4.2.2 Description and mechanism of action of Ascorbic Acid

The mechanism of action of ascorbic acid-mediated tumor suppression appears to depend on hydrogen peroxide production in extracellular fluid; hydrogen peroxide induces necrosis in tumor cells but not in normal cells.[8] Ascorbic acid treatment inhibits prostate cancer cell growth through three mechanisms: (1) ascorbic acid induces H_2O_2-dependent cytotoxicity in prostate cancer cells, (2) ascorbic acid treatment decreased ATP levels in prostate cancer cells, and (3) ascorbic acid treatment induced autophagy in prostate cancer cells.[9] Ascorbic acid treatment also suppresses metastases in hormone-refractory prostate cancer.[10] Cytotoxicity of ascorbic acid requires mM concentrations.[11] The dose response curve for ascorbic acid on DU-15 and PC-3 prostate cancer cells, shown below (Source: Levine, NCI Developmental Therapeutics Program NSC 33832), demonstrate that ascorbic acid was more effective for DU 145, with nearly complete kill at 10 mM and produced no growth for PC3.

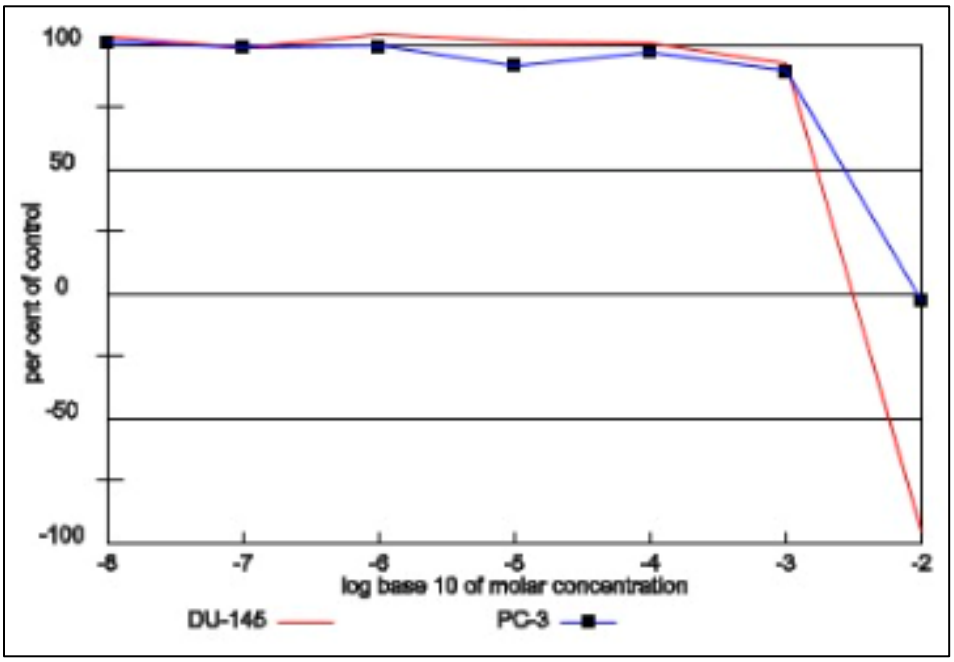

Figure 2: Dose response curve for ascorbic acid in DU-15 and PC-3 prostate cancer cells (Source: Levine, NCI Developmental Therapeutics Program NSC 33832)

Bioavailability of ascorbic acid is tightly controlled in response to oral administration and reaches only 100 µM with consumption of five servings of fruits and vegetables, which contain approximately 250 mg of ascorbic acid. Oral supplementation even at many grams does not increase plasma concentration beyond 250 µM. IV administration bypasses the tight controls found with oral administration, and produces pharmacological ascorbic acid concentrations of 25-30 mM.[12] Pharmacological ascorbic acid concentrations of 10mM can be maintained for approximately 4 hours with infusion rates of 0.5 – 1.0 g/kg per minute.[13,8]

4.2.3 Preclinical studies of Olaparib

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.[14] Efficacy in 22Rv1 cell line xenografts was similarly seen with olaparib in a separate study.[15] These included PC3 cells[14] and LNCaP cells.[16]

4.2.4 Preclinical studies of Ascorbic acid

Gulo$^{-/-}$ murine models are deficient in the enzyme responsible for in vivo ascorbic acid synthesis, mimicking human's need for an exogenous source of ascorbic acid. In a hepatoma xenograft *Gulo*$^{-/-}$ mouse model, ascorbic acid given orally did not inhibit tumor growth. However, parenteral ascorbic acid was successful in inhibiting tumor

growth in these mice.[17] This preclinical evidence provides support for intravenous infusion of ascorbate.

Linus Pauling first considered ascorbic acid as a treatment for cancer in the early 1970s. However, this research stalled for several years after investigators at the Mayo Clinic found cancer treatment with oral ascorbate to be ineffective.[18] Recent insight into the pharmacokinetic properties of ascorbate revealed that ascorbate must be administered intravenously in order to achieve plasma concentrations necessary to effectively kill cancer cells. With a renewed focus on intravenous dosing, ascorbate has proved to be lethal to and highly selective for a variety of cancer cell types.[11] There are several mechanisms currently under investigation to explain how ascorbate exerts anti-cancer effect; however, a simplified model depicts ascorbate as a pro-drug for reactive oxygen species (ROS), which accumulate intracellularly and generate DNA damage.[19] The complete pre-clinical experience is described in the current version of the Ascorbic Acid Investigator's Brochure (IB).

4.2.5 Preclinical evidence to support combination Olaparib and Ascorbate
Combination IV ascorbate and PARP inhibitors shows synergy of antitumor activity in two CRPC xenograft models, C4-2 and 22Rv-1. These results are shown in figures 2 and 3.

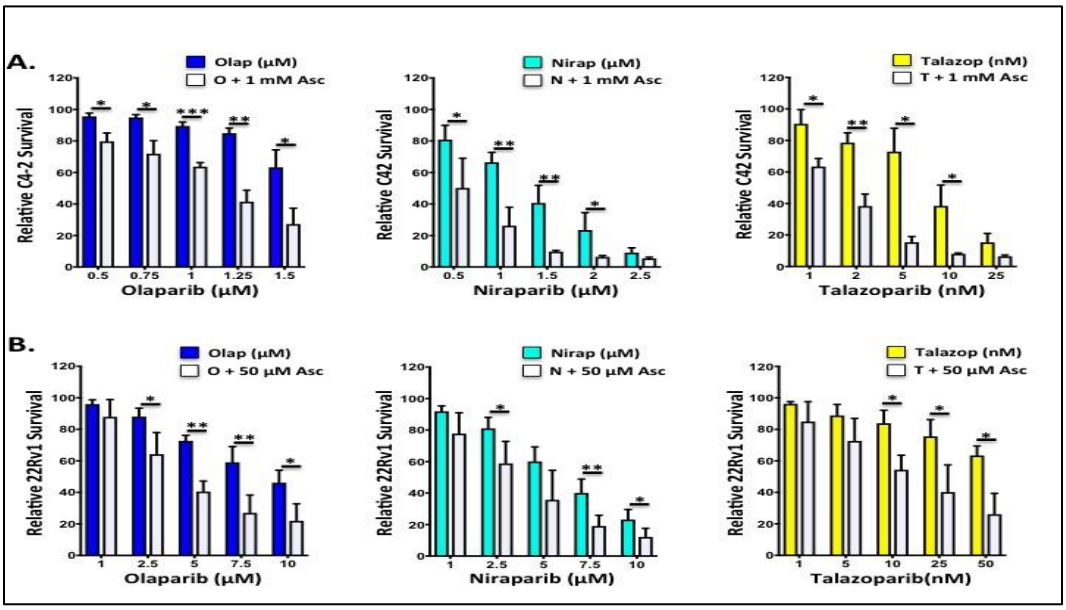

Figure 3. Ascorbate enhances the killing of C4-2 and 22Rv1 cells by PARP inhibitors. A) C4-2 cells were seeded in IMEM and allowed to settle overnight. They were then treated with a range of doses for three different PARP inhibitors: olaparib (left), niraparib (middle), and talazoparib (right) either alone or in combination with a sub-lethal dose of ascorbate (1mM). B) 22Rv1 cells were seeded in DMEM and allowed to settle overnight. They were then treated with a range of doses for the same three PARP inhibitors either alone or with a sub-lethal dose of ascorbate (50μM).[20]

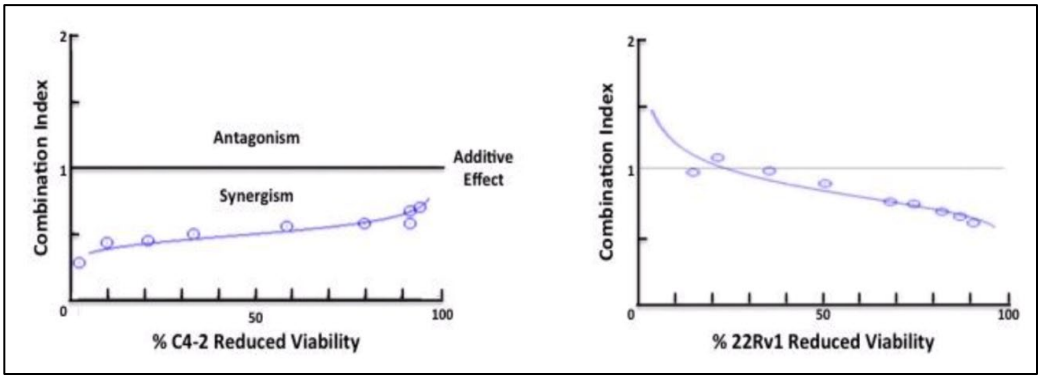

Figure 4. CompuSyn was used to generate a combination index. >1 denotes antagonism, =1 denotes an additive effect, <1 denotes synergism[20]

An *in vivo* model (figure 4) demonstrated that the combination of olaparib and ascorbate significantly slowed tumor growth compared to vehicle controls and monotherapy (results shown in figure 5). [20]

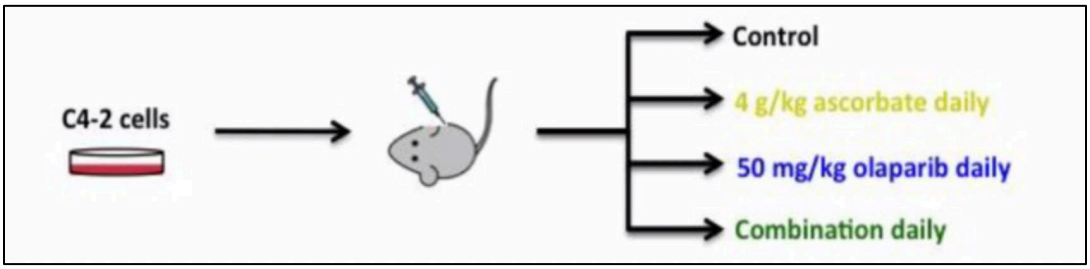

Figure 5: *In vivo* model of C4-2 cells, transplanted into mice and exposed to 4g/kg ascorbate daily, 50 mg/kg olaparib daily, a combination of the two agents daily, or a control[20]

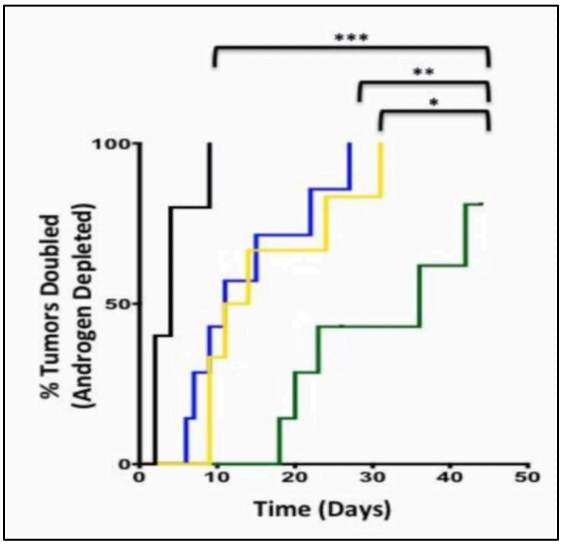

Figure 6: *In vivo* efficacy was profound in a model using castrated mice to mimic the effect of hormone therapy. While there was some antitumor effect with the single agents, there was a significant delay in tumor doubling time when the agents were used in combination.[20]

4.2.6 Clinical Efficacy and Safety of Olaparib

Many trials have studied the clinical efficacy and safety of olaparib. The complete clinical experience with olaparib, including toxicology and safety pharmacology, 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.[5] In a follow-up study of patients with germline BRCA mutations, 8 prostate cancer patients were included.[21]

Recently, a larger cohort of prostate cancer patients treated with olaparib was published.[22] 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).[22] Eleven of 49 evaluable patients experienced a greater than 50% decline in PSA (a PSA_{50} 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 mutation.

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

Clinical Studies in All Diseases

The largest pool of data for olaparib is drawn from a phase II trial of patients with germline deleterious BRCA 1 or 2 mutations.[21] 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-approved 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 in Table 1 below:

Table 1. Events occurring in >15% (any grade) or >5% (grade 3-4) in the trial.[21]

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

4.2.7 Clinical Efficacy and Safety of IV Ascorbic Acid

Multiple phase I trials of IV ascorbic acid safety and phase I/II trials of IV ascorbic acid safety and efficacy in cancer patients have been published. In one trial ascorbic acid in elderly patients with advanced cancer who had failed all other therapies, 2 patients had unexpectedly stable disease after 8 weeks of ascorbic acid treatment.[13] In a trial of patients with metastatic stage 4 pancreatic cancer who received primary therapy with ascorbic acid, gemcitabine, and erlotinib, 8 of 9 patients had tumor shrinkage after 8 weeks of therapy as measured by CT imaging.[23] A phase I trial of patients with metastatic stage 4 pancreatic cancer who were treated with gemcitabine + IV ascorbic acid as primary therapy until tumor progression showed few toxicities associated with the treatment. The 9 patients had a tripling of disease free internal in comparison to literature controls, and doubling of survival compared to retrospective controls.[24] In a dose escalation study, no toxicity was found at doses even above 1.5g/kg, the doses used in the other three trials.[25] In addition, a phase I/II trial of high-dose, IV ascorbic acid reduced grade 1 and 2 toxicities associated with carboplatin and paclitaxel treatment by more than 50% in women with ovarian cancer in a small, randomized clinical trial. Patients receiving IV ascorbic acid reported lower levels of low-grade gastrointestinal, hepatobiliary, dermatological, immune/infection, pulmonary and renal toxicities commonly associated with carboplatin and paclitaxel treatment.[26] A trial enrolling women with breast cancer randomized to IV ascorbic acid or placebo, in the first year following surgery, showed significant reductions in nausea ($p=0.022$), loss of appetite ($p=0.005$), fatigue ($p=0.023$), dizziness ($p=0.004$) and hemorrhagic diathesis ($p=0.032$). Reduced toxicities were experienced by patients independent of whether they were being treated with chemotherapy.[27] Similarly, a phase I/II study of arsenic trioxide/bortezomib/ascorbic acid combination therapy for the treatment of relapsed or refractory multiple myeloma with ascorbic acid IV on days 1, 4, 8, and 11 demonstrated a response rate of 27% in a heavily pretreated population. Ascorbic acid demonstrates activity at twice a week dosing.[28] Taken together, these data support the starting dose of 1g/kg of ascorbic acid in patients with CRPC and mCRPC.

Intravenous ascorbic acid is in wide use by practitioners of complementary and alternative medicine. Estimates are that in the US approximately 10,000 patients receive IV ascorbic acid each year at average doses of 0.5/kg, with average number of doses of twenty per patients. Using multiple tracking mechanisms, minimal adverse events were reported in properly screened patients.[29]

4.2.8 Clinical efficacy and safety of combination Olaparib and IV Ascorbate
This trial seeks to assess the combination of olaparib and IV ascorbic acid in men with castration resistant prostate cancer. There is no clinical data to support this combination at this time as these two agents have not been combined in the past to treat castration resistant prostate cancer. The CRPC patient population is in desperate need of new treatment options, and the *in vitro* and *in vivo* data suggest that the combination of olaparib and ascorbate may be effective. The proposed clinical trial aims to determine the safety, tolerability, and provide preliminary data on efficacy of combining olaparib with intravenous ascorbate for the treatment of advanced prostate cancer.

A drug-drug interaction between ascorbic acid and olaparib is not anticipated based on drug metabolism and drug transporters. Olaparib metabolism is primarily mediated by CYP3A4/5. Clinical drug-drug interactions have been noted with strong or moderate CYP3A4 inhibitors or a moderate CYP3A4 inducer. Olaparib is a substrate for Pgp. Olaparib is an inhibitor of CYP3A4, UGT1A1, Pgp, OATP1B1, OCT1, OCT2, OAT3, MATE1, and MATE2K in vitro. Olaparib is an inducer of CYP1A2, CYP2B6 (potentially clinically relevant), CYP3A4, and P-gp. Ascorbic Acid is reversibly oxidized to dehydroascorbic acid (DHA) and metabolized to inactive compounds including ascorbic acid-2-sulfate and oxalic acid. No drug interactions have been noted via the CYP450 pathway. Ascorbic acid is a substrate of two sodium-ascorbate co-transporters (SVCT; both members of the SLC23 family).[30] Oxalic acid is a substrate of OAT3[31] and inhibitor of OATP1B1[32]. There is a potential for an interaction via the drug transporters at the oxalic acid level but would not be anticipated to be clinically relevant. Therefore, a formal pharmacokinetic assessment will not be conducted.

4.3 Rationale for combination Olaparib and Ascorbic Acid

There is significant evidence supporting single agent tumor stability of olaparib in DNA repair mutant prostate cancer and of the effectiveness of ascorbate in reducing toxicities of chemotherapy. The ability to manipulate DNA damage repair has made PARPi an attractive option for combination with DNA damaging agents, such as ascorbate. We therefore hypothesize that ascorbate's ability to generate damage-inducing ROS would benefit from the addition of a PARP inhibitor designed to impede a tumor cell's ability to repair DNA damage. Historically, response to olaparib was 88% in HRD+ and 6% in HRD- mCRPC patients.[22] Per the data described in **Section 4.2**, as well as data from Ma et al[26], we hypothesize that the combination of olaparib and ascorbic acid will synergize and increase efficacy to be greater than 6% with acceptable toxicities.

5.0 PATIENT SELECTION

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if they meet ***all*** of the following criteria:

[1] Have metastatic castration-resistant prostate cancer (prostate cancer progressing by PSA (rise by 25% on prior therapy) or imaging despite castrate levels of testosterone [<50 ng/dL] using standard measures of progression defined by Prostate Cancer Working Group[33]).

[2] Have a minimum PSA of 1 ng/mL.

[3] Have a pathological diagnosis of prostate carcinoma.

[4] Have been receiving and will continue to receive continuous hormonal ablation with surgical or medical castration with baseline testosterone <50ng/dL.

[5] May be receiving bone-targeted agents.

[6] May have received multiple lines of therapy including radium 223, sipuleucel T, and up to 2 lines of chemotherapy (One of 2 lines may be for hormone sensitive metastatic prostate cancer or both can be for castration resistant).

[7] Age $\geq$ 18.

[8] Have ECOG performance status 0-1 **(Appendix A)**.

[9] Be able to take oral medication and willing to consider a port for ease of administration of ascorbate.

[10] Must have progressed on one systemic line of treatment (can include LHRH agonist/antagonist or orchiectomy and at least one additional line of therapy (abiraterone, enzalutamide, apalutamide, darolutamide, docetaxel, etc)).

[11] Have normal organ and marrow function measured within 28 days prior to administration of study treatment as defined below:

- Absolute neutrophil count	>1.5 x 10^9/L
-Platelets	$\geq$ 100,000/mm^3
-Hemoglobin	$\geq$ 9g/dL with no blood transfusion in the past 28 days
-Total bilirubin	$\leq$ 1.5 x ULN
-AST (SGOT)/ALT(SGPT)	$\leq$ 2.5 x ULN (<5x ULN if with known liver metastases provided bilirubin is normal
-Creatinine	$\leq$ 1.6 x ULN (for patients with $\geq$1.6 x ULN, calculated or measured creatinine clearance must be $\geq$ 60 mL/minute (Cockcroft-Gault).

[12] Men of reproductive potential and those who are surgically sterilized (i.e. post-vasectomy) must agree to practice effective barrier contraception that has an expected failure rate of <1% during and for 6 months after discontinuation of study treatment. Female partners should also use a highly effective form of contraception ([see **Appendix C** for acceptable methods]) if they are of childbearing potential.

- If condoms are used as a barrier contraceptive, a spermicidal agent should be added to ensure that pregnancy does not occur.

[13] Have the ability to understand and have given written informed consent before performance of any study-related procedures not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

5.2 Exclusion Criteria

Patients are ineligible to be included in the study if they:

[1] Have a known DNA repair mutation (minimum list of genes that must be mutation negative for inclusion: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L). In addition, patients who have not completed germline and somatic testing to rule out such a mutation are ineligible until they have completed testing. If tissue or liquid ctDNA sequencing was not previously done, testing using the Foundation One liquid biopsy test or an equivalent FDA-approved test is acceptable as standard of care.

- DNA repair mutation variant of unknown significance (VUS) allowed.

[2] Have had known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

[3] Have symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

[4] Have had prior olaparib, rucaparib, or other PARP inhibitor.

[5] Have had major surgery within 2 weeks of dosing of investigational agent.

[6] Have had palliative radiation or another biological cancer therapy within 3 weeks prior to the first dose of study drug (2 week wash out required).

[7] Are receiving any systemic chemotherapy or radiotherapy within 3 weeks prior to study treatment.

[8] Have received other investigational drugs within 14 days prior to enrollment.

[9] Is expected to require chemotherapy or radiation for pain palliation in the next 12 weeks.

[10] Have used or plan concomitant use of the following medications in the past 6 months prior to enrollment: 5-alpha reductase inhibitors unless subject has been taking stable dose of medication for prior 6 months.

[11] 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 study treatment is 2 weeks. See the following link for a complete list of known CYP3A inhibitors:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

[12] Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. See the following link for a complete list of known CYP3A inhibitors:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

[13] Have moderate or severe cardiovascular disease:

- Has the presence of cardiac disease, including a myocardial infarction within six months prior to study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension.
- Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTc prolongation >500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.

[14] Have uncontrolled intercurrent illness, including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

[15] Have other malignancy unless curatively treated with no evidence of disease for ≥5 years except adequately treated non-melanoma skin cancer.

[16] Have persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE v5.0) grade 2) caused by previous cancer therapy, excluding alopecia.

[17] Patients with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

[18] Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples

include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

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

[20] Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV).

[21] Patients with known active hepatitis (i.e. Hepatitis B or C).

[22] Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).

[23] Patients with a known hypersensitivity to olaparib or any of the excipients of the product.

5.3 Inclusion of Minorities and Women and Children

Since prostate cancer is only a disease of men, only male patients will be enrolled. Men from all ethnic groups are eligible for this trial. The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins serves a prostate cancer population in which approximately 25% of these patients are African Americans. We anticipate that enrollment in this study will be reflective of our usual patient population. Minority patients who meet the eligibility requirements will be actively recruited to participate in the study. This study was designed to encourage minority accrual but was not designed to measure differences in racial or ethnic populations.

6.0 REGISTRATION

6.1 General Guidelines

Potential study subjects will be identified and screened by the study team. Eligible patients will be consented prior to treatment initiation. Eligible, consented patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins by the Lead Study Coordinator. Patient names and identifying information will only be linked in the CRMS (Clinical Research Management System) database, which is accessible through a password-protected encrypted university server. All sites should email Harry Cao hcao7@jhmi.edu to verify slot availabilities.

Issues that would cause treatment delays should be discussed with Dr. Paller. If a patient does not receive protocol therapy within 7 days following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

6.2 Registration Process

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Lead Study Coordinator. All sites should email Harry Cao at hcao7@jhmi.edu to verify drug availabilities. The Registration Form, and Eligibility Worksheet will be supplied to each participating site.

If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Coordinating Center should be notified of cancellations as soon as possible.

To register an eligible, consented patient, the following documents should be completed by the Research Nurse or Study Coordinator and emailed to the monitors Harry Cao at hcao7@jhmi.edu.

- Signed patient consent form
- Eligibility Screening Checklist
- Copies of the prostate cancer pathology report
- Copies of PSA and Testosterone results to determine eligibility
- Copy of required screening labs and scans
- Physician note that indicated prior therapies
- Other materials may also be sent if considered pertinent for confirming patient eligibility

The Research Nurse or Study Coordinator at the participating site will then email the monitors to verify eligibility. To complete the registration process, the monitors will:

- Assign a patient study number
- Register the patient on the study
- Email the registration confirmation to the participating site

7.0 TREATMENT/INTERVENTION PLAN

The following assessments and procedures will occur during the study. A schedule of assessments is provided in **Section 7.1**

7.1 Study Calendar

Required Studies	Pre-study [14]	1 cycle = 28 days					EOT[14, 16]	LONG TERM FU[17]
	Screening	C1D1[14, 15]	C1D8	C1D15[14]	C1D22[14]	CnDn[20]		
Visit Windows (days)[1]	-28	+/-3	+/-3	+/- 3	+/- 3	+/- 3	-28	+/-28
TREATMENT								
Olaparib		X	X	X	X	X		
Ascorbic acid[2,3]		X	X	X	X	X		
ELIGIBILITY								
Inclusion/exclusion review	X							
HRR status[19]	X							
Informed consent	X							
ECG	X							
PHYSICAL								
Medical and Cancer History	X							
Physical Exam, Weight and ECOG[4]	X	X	X	X	X	X	X	X
Vital Signs[5]	X	X	X	X	X	X	X	X
AE/Toxicity Notation[4]		X	X	X	X	X	X	X
Concurrent meds[4]	X	X	X	X	X	X	X	X
LABORATORY								
Chemistry[6,7]	X	X	X	X	X	X[7]	X	X
Hematology[6,7]	X	X				X[7]	X	X
Urinalysis	X							
INR and PT/APTT[18]	X							
Urine Creatinine[8]	X[8]	X[8]				X[8]	X[8]	
Testosterone	X							
PSA[7]	X	X				X[7]	X	X
G6PD[9]	X							
CORRELATIVE								
Blood Samples[10, 12]	NA	X[10]				X[10]	X[10]	
Urine Samples[11, 12]	NA	X[11]				X[11]	X[11]	
Optional Biopsy (Encouraged)	X[12]	N/A				X[12]		
DISEASE ASSESSMENT								
Radiologic Evaluation/ RECIST 1.1[13] or PCWG2	X[13]					X[13]	X[13]	
LONG TERM FOLLOW-UP[17]								X[17]

[1] Longer delays to be approved by the study sponsor. IRB approval is required for all eligibility waivers prior to enrollment. The window for the baseline Radiologic Evaluation/RECIST 1.1 is 6 weeks prior to C1D1.

[2] Each treatment cycle is 4 weeks (28 days). Ascorbic Acid dosing must be 2 times per week except week 1 when Olaparib is giving alone. The first infusion must occur on day 1 of each cycle and the second infusion can occur any other day during the week as long as it is at least 24 hours from the prior infusion.

[3] Ports are recommended but not mandatory due to the frequency of infusion.

[4] After screening, physical exams may be limited as indicated by symptoms. ECOG – Eastern Cooperative Oncology Group performance status. Physical exam (including vital signs and weight), ECOG status, AE/Toxicity notation and concurrent medication review have a -3 day window of day 1 of the cycle.

[5] Vital signs will be collected prior to infusion. Vital signs include temperature, blood pressure, respiration rate, and heart rate. Height is collected pre-study only. There is a -3 day window of day 1 of each cycle that the vital signs can be collected within.

[6] Clinical Hematology: CBC with differential ANC, ALC, AEC, and platelet count; Serum Chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, calcium.

[7] Safety labs and PSA may be collected within a window of up to 3 days prior to scheduled visit/dosing. As of Cycle 2 and further cycles: at Day 1 visit, hematology and chemistry should be collected per hold parameters; at Days 8, 15, and 22 visits, only chemistry will be collected per hold parameters (hematology does not need to be drawn on Days 8, 15, and 22 unless clinically indicated). After C1D1, PSA is collected at CnD1 only (i.e., not weekly).

[8] Urine creatinine will be collected at C1D1, C2D1 (4 weeks), C4D1 (12 weeks), and at EOT.

[9] G6PD testing: Red blood cell hemolysis may occur in people found to be deficient in the G6PD enzyme.

[10] Up to 50mL of whole blood will be collected for ctDNA analysis at each time point. Blood samples should be drawn at screening (or pre-dose C1D1), C2D1 post infusion (4 weeks), C4D1 (12 weeks) post infusion, and at EOT. Bloods do not need to be collected at C1D1 if they were collected within 7 days prior to the visit. γ H2AX will also be assessed at C1D1, C1D8, C2D1, C4D1 and progression.

[11] Urine samples of up to 15mL will be collected to assess F2-isoprostanes and 8-oxo-2'-deoxyguanosine at screening (or pre-dose C1D1), C2D1 (4 weeks), C4D1 (12 weeks), and at EOT. Urine samples do not need to be collected at C1D1 if they were collected within 5 days prior.

[12] Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff. An optional biopsy at baseline and at C4D1 (+/- 2 weeks) will be performed to look for γH2AX in tissue.

[13] CT scan (chest/abdomen/pelvis or MRI if patient has contrast allergy) and bone scan to be assessed at baseline and every 12 weeks (+/- 1 week), and at EOT (if clinically indicated by PI/Sub-I).

[14] In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person 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 methods approved by the Health System and within licensing restrictions.

[15] There is a -7 day window to draw C1D1 labs.

[16] The EOT visit must occur within 28 days of the last dose of ascorbic acid or olaparib, whichever is later.

[17] Subjects who discontinued study treatment without documented disease progression should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed every two months (+/- 2 weeks) until: 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) study closure, whichever occurs first. Survival status and subsequent therapies will be collected during long term follow-up (LTFU) every 6 months (+/- 4 weeks) from the date of last treatment, by phone or chart review, for 3 years or until study closure. Gather date of death, date of radiographic and/or PSA progression, start and stop dates for subsequent therapies.

[18] INR and PT/APTT will be performed at baseline and at subsequent timepoints if clinically indicated.

[19] HRR status will be determined by evaluating patients for mutations in the genes ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L. DNA repair mutation variants of unknown significance will be allowed. Mutation status of these genes will be determined with standard of care tests, such as Invitae, Color, or Foundation One, using germline and somatic testing. Tissue (prostatectomy or metastatic biopsy for somatic or germline testing), blood (somatic or germline) or saliva (germline) are all acceptable for standard of care testing prior to enrollment. Germline test results will be confirmed with somatic testing. If tissue is not available, confirmation testing using Foundation One liquid biopsy test or an equivalent FDA-approved test is acceptable. The type of test and results for each individual patient will be captured in the appropriate CRF in the database.

[20] For all subsequent cycles, patients will repeat the four visits listed for Cycle 1 (CnD1, CnD8, CnD15, CnD22).

7.2 Screening/Pretreatment Assessment (up to Day -28)

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 to 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 following assessments will be performed at the screening 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, and history of radiation therapy or other local therapy).
- Obtain histologic/radiographic confirmation of disease. If radiographic studies have not been performed within 6 weeks prior to Cycle 1 Day 1, they must be obtained as part of screening.
- Perform laboratory tests: complete blood count w/diff, PSA, comprehensive metabolic panel, urinalysis, G6PD, testosterone.
- Baseline ECG
- Confirmation of 25% PSA rise on prior therapy.
- Determine suitability for olaparib and ascorbate therapy.
- Discuss concurrent medications.

Relevant information should be documented for registration and monitoring purposes. The institutional registration should be finalized, and appropriate documents faxed or emailed to the lead site/sponsor per **Section 6.0**.

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

For any subject that has a DNA repair gene mutation identified during screening and is therefore not eligible for this trial 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.

7.3 Treatment/Intervention Period

Patients will be seen on D1 of each cycle of study therapy (consisting of 28 days $\pm$3 days). The following assessments will be performed at each visit:

- Conduct physical exam (including vital signs, weight)
- Obtain and medical history changes from prior assessment
- Assess performance status (ECOG). **(Appendix A)**
- Review concurrent medications

7.3.1 Clinical, Laboratory, and Radiographic Assessments

Every week, patients will have a non-fasting blood drawn for the values listed below. Repeat labs are not needed on C1D1 as long as visit is within 7 days of screening visit blood draw.

- CMP

Note: Patients with creatinine clearance between 51-100 mL/min either at trial enrolment or during the course of the trial should be monitored every week for laboratory assessment and toxicity evaluation.

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

- CBC
- PSA

Every 3 cycles, patients will have radiographic studies:

- CT chest, 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 Day 1 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. Patients taking warfarin may not participate in this study.

Biochemistry assessments for safety (sodium, potassium, calcium, glucose, creatinine, total bilirubin, gamma glutamyl transferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin) should be performed at each Day 1, Day 8, Day 15, and Day 22 visit.

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

Bone marrow or blood cytogenetic samples may be collected from patients with prolonged hematological toxicities as defined under **Section 8.2.2.3** *Dose Modifications for Toxicities.*

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 D '**Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

7.3.2 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 the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

7.3.3 Study Treatment

Treatment information is detailed in Agent Administration (Section 7.6).

7.4 Duration of Therapy and Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed apply. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression by RECIST criteria v1.1 (**Appendix E**) or bone progression per PCWG3 (see **Section 7.4.1**)
- Disease progression by symptomatic 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 (see **Section 7.4.1**)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s): toxicity (defined in **Section 8.1**) that has not recovered in 2 weeks or if the same toxicity recurs at the decreased dose (unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment, and the rationale must be discussed with the Principal Investigator before a decision is made)
- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- If, in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the subject
- Patient is noncompliant with respect to taking drugs, keeping appointments, or having tests required
- for the evaluation of drug safety and efficacy Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Potential Hy's Law cases (AST or ALT ≥3x ULN and TBL ≥2x ULN with no other reason)

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.

7.4.1 Disease Progression

Progression will be evaluated on the basis of biochemical, radiographic, or symptomatic progression based on PCWG3 criteria, or by PSA doubling from baseline. Determinations of disease progression will be made by the investigator.

Progression will be defined as follows:

1. Radiographic progression defined by at least one of the following:
   - Soft tissue disease progression by modified RECIST criteria v.1.1 (See **Appendix E**)
   - Development of two or more new bone lesions not consistent with tumor flare per PCWG3. (If unclear, can repeat a bone scan in 6 weeks.)
2. Symptomatic or clinical progression defined by one of the following:
   - Development of a skeletal related event (SRE) defined as pathologic fracture, spinal cord or nerve root compression, palliative radiation to bone, or surgery to bone
   - Worsening pain due to CRPC unable to be controlled by non-narcotic or narcotic medications
   - Sustained worsening of ECOG status resulting from CRPC (e.g., 2 to 3)
   - Treating physician decided to initiate new systemic anti-cancer therapy
3. 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

We will encourage investigators to continue study treatment until radiographically confirmed disease progression or PSA doubling from baseline requires initiation of new systemic antineoplastic therapy.

7.4.2 EOT Visit

Upon treatment discontinuation, patients will have an EOT Visit within 28 days of the last dose of ascorbic acid or olaparib, whichever is later. This visit will consist of the following:

- Conduct physical exam (including vital signs, 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 C/A/P and NM bone scan (if these have not been performed in the prior 3 months)
- Blood and urine research samples

7.5 Duration of Follow Up

Subjects will be followed for adverse events for a minimum of 30 days after the last dose of study drug or death, whichever occurs first. Subjects removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event, initiation of new therapy for their cancer, or death, whichever occurs first.

Subjects who discontinued study treatment without documented disease progression should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed every two months (+/- 2 weeks) until: 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) study closure, whichever occurs first.

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of cancer, after discontinuation of treatment, may 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.

7.5.1 Long Term Follow-Up

Survival status and subsequent therapies will be collected during long term follow-up (LTFU) every 6 months (+/- 4 weeks), by phone or chart review, for 3 years or until study closure. Additionally, the following data will be collected: date of death, date of radiographic and/or PSA progression, start and stop dates for subsequent therapies.

7.6 Agent Administration

Treatment will be administered on an outpatient basis. Expected adverse events and potential risks are described in **Section 7.9.** Appropriate delays and modifications are described in **Section 8.1** and **Section 8.2**, respectively**.** Events that result in dose adjustments for each drug (i.e. 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, are considered treatment-limiting adverse events. Treatment-limiting adverse events for ascorbic acid and olaparib are described in **Section 8.1**. No investigational or commercial agents or therapies older than those described below may be administered with the intent to treat the subject's malignancy. The drug regimen for this trial is shown below in **Table 2**.

Table 2: Regimen Description

Regimen Description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Olaparib[1]	300 mg	Oral	Twice daily, days 1-28	28 days (4 weeks)
Ascorbic Acid	1 g/kg [2]	0.75-1 gram per minute IV[3]	Twice weekly[4] First dose on day 1 of the cycle	

1. Olaparib: two 150 mg tablets orally, with or without food, twice daily. The tablets are to be swallowed whole (do not chew, dissolve, or open the tablets). Administration should be in accordance with the package insert.[34]
2. For a subject weighing 75 kg, the goal dose is 75 grams (1 g/kg), and the titrated dose schedule is 18.75 g, 37.5 g, and 56.25g for cycle 1 only. Rounding the calculated doses to 19 g, 38 g, and 56 g is acceptable. Subsequent doses would be 75 g. The maximum allowed dose for patients weighing over 100 kg is 100 g.
3. Infusion time is approximate (± 15 minutes) and may need to be adjusted based on patient tolerability. Infusion time is estimated to be between 90-120 minutes.
4. The ideal schedule for ascorbic acid is 3-4 days apart for administration. However, ascorbic acid can be safely administered on consecutive days (at least 24 hours apart). The day that ascorbic acid can be administered can be shifted in the event of holidays, inclement weather, and other reasons for clinic closure to even three consecutive days.

Subsequent ascorbic acid infusions may not be given less than 24 hours apart.

Acute reactions will be managed using standard therapy for acute drug reactions as per institutional standard of care.

7.6.1 Olaparib Administration

Patients will be administered olaparib twice daily at 300mg continually. Two 150mg olaparib tablets should be taken twice daily at the same time each day, 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.

7.6.2 Ascorbic Acid Administration

For the first cycle, on cycle 1 day 8, collect blood for CTCs and then start Ascorbic Acid. The first three doses of ascorbic acid will be titrated as such: 0.25 g/kg, 0.5 g/kg, 0.75 g/kg in 1000ml of sterile water (not to exceed 500 mL per hour). If tolerated, the subsequent doses will be 1 g/kg. Infusions will be twice a week, and should not be less than 24 hours apart. It is recommended that ascorbic acid be given through a port due to frequency of infusion, but a port is not required.

7.7 Concomitant, Supportive, and Restricted Medication and Supportive Care Guidelines

The use of any natural/herbal products other than traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded in the case report form (CRF), along with reason for use, dates of administration including start and end dates, and dosage information including dose and frequency. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Principal Investigator or Co-Investigators. Concurrent treatment with bisphosphonates is allowed. All concomitant treatments, including blood and blood products, must be reported on the case report form (CRF).

In order to better differentiate adverse events related to investigational study agents from those related to the COVID-19 vaccine, it is recommended where possible, that subjects not receive any dose of the COVID-19 vaccine within 3 days of study drug. If a live COVID-19 vaccine becomes available to the public, an exemption specifically for live COVID-19 vaccines will be discussed with the Protocol Manager.

Restricted concomitant medications

Medications prohibited 6 months prior to enrollment

5-alpha reductase inhibitors are allowed if subject has been taking stable dose of medication for prior 6 months.

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. See this link for a complete list of known CYP3A inhibitors: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. During the study, if co-administration or a strong or moderate inhibitor is required because there is no suitable alternative medication, dose of olaparib should be reduced for the period of concomitant administration.

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg twice daily for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards.
- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards.
- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

Strong or moderate CYP3A inducers

Strong (e.g. phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St. John's Wort) and moderate (e.g. bosentan, efavirenz, modafinil) CYP3A inducers should not be taken with olaparib. See this link for a complete list of known CYP3A inhibitors: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Effect of olaparib on other drugs

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

Based on limited in vitro data, olaparib may reduce the exposure to substrates of 2B6 (and potentially substrates of CYP2C9, CYP2C19 and P-gp).

Caution should be observed if statins or sensitive CYP3A4 substrates are co-administered.

Appropriate clinical monitoring is recommended for patients receiving P-gp substrates or CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.

Examples of substrates include:

- CYP3A4 substrates with narrow therapeutic margin: e.g. cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and warfarin.
- Sensitive CYP3A4 substrates: e.g. buspirone, felodipine, fluticasone, lovastatin, quetiapine, saquinavir, sildenafil and simvastatin.
- CYP2B6 substrates: e.g. bupropion and efavirenz.
- OATP1B1 substrates: e.g. bosentan, glibenclamide, repaglinide, statins and valsartan.
- OCT1, MATE1 and MATE2K substrates: e.g. metformin.
- OCT2 substrates: e.g. cimetidine and metformin.
- OAT3 substrates: e.g. furosemide and methotrexate.
- BCRP substrates: e.g. methotrexate and rosuvastatin.
- P-gp substrates: e.g. simvastatin, pravastatin, dabigatran, digoxin and colchicine.

Anticoagulant Therapy

Patients who are taking warfarin may not participate in this trial due to potential warfarin resistance due to its interaction with ascorbic acid.[35,36] Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin and low molecular weight heparin may be given concomitantly with olaparib and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (e.g. apixaban and rivaroxaban) if possible.

Anti-emetics/Anti-diarrheals

If a patient develops nausea, vomiting, and/or diarrhea, then these symptoms should be reported as AEs (see **Section 9.5**) 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. 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.

Vaccines

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.

Other prohibited products

It is prohibited to consume grapefruit juice while on olaparib therapy. Patients must not consume grapefruit or Seville oranges while on treatment with olaparib.

See **Table 3** for summary of Prohibited Medications.

Table 3: Prohibited medications

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

7.8 Contraception

Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (as described in **Appendix C**) if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

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

7.9 Expected Adverse Events

7.9.1 Ascorbic Acid

Too rapid intravenous administration of the solution may cause temporary faintness or dizziness.

<u>The most common side effects of ascorbic acid include:</u> pain and swelling at administration sites, nausea, vomiting, diarrhea, dry mouth, loss of appetite, muscle weakness, dizziness, headache, phlebitis, hypertension, fatigue, and leakage of protein.

<u>Less common side effects of ascorbic acid include:</u> acute and chronic nephropathy, kidney stones, renal failure, hypernatremia, hypoalbuminemia, hyperglycemia, and hypokalemia.

Of note, it has been reported that patients with a history of glucose-6-phosphate dehydrogenase deficiency experienced hemolysis.

7.9.2 Olaparib

The most common side effects of olaparib include: nausea, fatigue (including asthenia), anemia, vomiting, diarrhea, decreased appetite, headache, neutropenia, dysgeusia, cough, dyspnea, dizziness, dyspepsia, leukopenia, thrombocytopenia, and upper abdominal pain.

Less common side effects of olaparib include: constipation, lymphopenia, mean corpuscular volume [MCV] elevation, blood creatinine increased, hypersensitivity, dermatitis, stomatitis, MDS/AML, and rash.

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

7.10 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see **Section 9.5.1**).

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).

Overdose with ascorbic acid may cause nausea, vomiting, diarrhea, facial flushing, rash, headache, fatigue or disturbed sleep. If overdose of ascorbic acid occurs, immediately discontinue administration, avoiding additional intake of ascorbic acid until symptoms are managed appropriately.

Ascorbic acid 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 1 g/kg, with the maximum dose of 100 g for patients weighing over 100 kg.

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

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

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

8.0 DOSING DELAYS/MODIFICATIONS

8.1 Dosing Delays

All scheduled cycles occur over a 28-day period. If necessary, treatment may be delayed for up to 4 weeks. If treatment is delayed more than two weeks, the Principal Investigator must be contacted for further instructions on continued treatment. Additional delays or modifications to the treatment schedule must be approved by the Protocol Chair. When the delay is due to toxicity, then the next cycle may begin with a dose reduction.

Ascorbic acid will be withheld for the following drug-related toxicities:

- Cr ≥ 1.6 x ULN (for patients with Cr ≥1.6 x ULN, calculated or measured creatinine clearance must be ≥50 mL/minute (Cockcroft-Gault))
- Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 non-hematologic toxicity excluding asymptomatic electrolyte aberrations
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgement of the investigator, warrants delaying the dose of study medication

Olaparib will be withheld for the following drug-related toxicities:

- Absolute neutrophil count ≤ 750/ mm^3, see **Table 8**
- Platelets ≤ 75,000/mm^3, see **Table 8**
- Hemoglobin ≤ 8 hgb, If < 10, see **Table 7**
- Total bilirubin ≧ 1.5XULN
- AST (SGOT)/ALT(SGPT) ≧ 2.5 x ULN (<5x ULN if with known liver metastases provided bilirubin is normal)
- Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 non-hematologic toxicity excluding asymptomatic electrolyte aberrations
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgement of the investigator, warrants delaying the dose of study medication

If dosing parameters for Ascorbic Acid are not met, study participants may continue with olaparib therapy. If dosing parameters for olaparib or are not met, study participants may continue with Ascorbic Acid therapy. Dose interruptions are allowed as required, for a maximum of 4 weeks. Patients who require an interruption in olaparib or ascorbic acid for >4 weeks due to toxicity must permanently discontinue study drug unless an exemption is granted by the protocol chair (Refer to section 13.6 for stopping rule). Where toxicity reoccurs following re-challenge with study treatment, then the patient should be considered for dose reduction or must permanently discontinue study treatment per investigator judgement.

8.2 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 7.3.1.** The NCI CTCAE v.5.0 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.

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

Patients who experience grade 3 of 4 toxicities (individually defined in **Section 8.1**) that are eligible for retreatment will be dose reduced. After a two-week dose delay, if the grade 3 or 4 toxicity resolves to grades 0-2 (grade 2 peripheral neuropathy must resolve to grade 1 if interfering with instrumental ADL), then the following dose reductions are to be applied.

8.2.1 Ascorbic Acid Dose Modification

One dose modification of ascorbic acid is allowed to 0.75 g/kg (if two dose reductions are required, the patient will go off protocol treatment).

Ascorbic acid dose modifications for symptoms other than grade 3 or 4 toxicities should be discussed with and approved by the Protocol Chair.

8.2.2 Olaparib Dose Modifications

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

It is recommended that known strong CYP3A inhibitors (eg, 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. If there is no suitable alternative concomitant medication, then the patient should discontinue protocol treatment.

8.2.2.2 Olaparib 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 (CrCl <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, it is recommended that olaparib be discontinued.

8.2.2.3 Olaparib 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 >4 weeks due to toxicity must discontinue all study therapy.

Olaparib can be dose reduced to 250mg twice daily as a first step and to 200mg twice daily as a second step with the exception of cases of CTCAE v5.0 grade 3 or 4 anemia when dose should be reduced to 200mg twice daily as first step. If the reduced dose of 200mg twice daily is not tolerable, no further dose reduction is allowed and all study treatment should be discontinued.

Once dose is reduced, escalation is not permitted.

For guidance on dose reductions for management of AEs (including renal impairment) refer to **Table 4 and Table 5**.

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

Table 4 Dose reductions for study treatment to manage adverse events

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

Table 5 Dose reduction for study treatment if patient develops moderate renal impairment

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

Table 6 Dose reductions for study treatment if patient has to start taking a strong or moderate CYP3A inhibitor

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

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided refer to **Table 6**.

When dose reduction is necessary patients will take one 150 mg tablet and one 100 mg tablet twice daily or two x 100 mg tablet twice daily or one 150 mg tablet twice daily or one 100 mg tablet twice daily.

Management of hematological toxicity

Management of anemia

Table 7 Management of anemia

Hemoglobin	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 8 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 grade 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 CTCAE 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 CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence

≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse neutropenia (ANC $<1 \times 10^9$/L)

≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets $<50 \times 10^9$/L)

Adverse events possibly must be resolved to grade 1 or baseline prior to resumption of dosing. Study treatment should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 4 weeks of dose interruption.

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-hematological toxicity

Dose interruptions are allowed as required, for a maximum of 4 weeks. Patients who require an interruption in study drug >4 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.

Olaparib can be dose reduced to 250mg bid as a first step and to 200mg 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 D** '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., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the 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 (i.e. 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 e.g. 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.

Renal Impairment

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

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24 hour urine test of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg twice daily.

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

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

9.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

9.1 Definitions

9.1.1 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). New medical conditions / diseases occurring before starting the study treatment but after signing the informed consent form will not be recorded as AEs. Additionally, expected progression of the disease being studied will not be recorded as an adverse event. 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.

9.1.2 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.

All SAEs (including death) occurring from the first dose study drug, throughout the study, and 30 days after the last dose of study drug or before initiation of a new antineoplastic treatment (whichever comes first) must be reported. All SAEs that the investigator considers related to the study drug occurring after the follow-up periods must be reported.

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 fulfills one or more of the following criteria:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions) for >24 hours
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Form)
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization), potential drug induced liver injury, hemophagocytic lymphohistiocytosis
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Is a new cancer that is not a condition of the study (see clarification below)
- Is associated with an overdose

Events **not** considered to be SAEs are hospitalizations for:

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
- Admissions for monitoring of treatment-related infusion reactions that do not otherwise meet the criteria for a SAE.

Hospitalization for chronic or long-term patients and inpatient admission also includes transfer within the hospital to an acute or intensive care inpatient unit. Prolongation of hospitalization is any extension of an inpatient hospitalization beyond the stay anticipated or required for the original reason for admission.

Of note, Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as Serious AEs.

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

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

9.1.3 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. Any AESI that occur should be reported using the form in **Appendix F**. 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 (e.g. 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.

9.1.4 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 study drug, progressive disease will be considered an SAE.

9.1.5 Significant disability

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

9.1.6 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 and McGuff.

9.1.7 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.

9.1.8 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.

When 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 an SAE within **24 hours** (see **Section 9.5.1** for further details). The report should contain a comment regarding the co-involvement of progression of disease, is 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 an SAE. A postmortem may be helpful in the assessment of the cause of death, and if performed a copy of the postmortem results should be forwarded to AstraZeneca and McGuff within the usual timeframes.

The NCI CTCAEv5.0 will be used for adverse event descriptions and grading.

Follow-up of adverse events should continue until the event and any sequel resolve or stabilize at a level acceptable to the investigator and the medical monitor.

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

- Routine treatment or monitoring of the studied indication, nor 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

9.2 Expectedness

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

9.2.1 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.

9.2.2 Unexpected Adverse Events

An adverse event can be considered unexpected when it varies in nature, intensity or frequency from the 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.

9.3 Recording and Grading

9.3.1 Recording

All 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 (i.e. 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.

The following factors should also be considered:

- The temporal sequence from study drug administration – The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases – Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant medication – The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug – Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses – The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug – The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

9.3.2 Grading Severity

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the eCRF. The assessment will be based on the National Cancer Institute's CTCAE (Version 5.0):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Any AE that changes in grade during its course will be recorded in the eCRF at the highest level experienced by the subject. For example, if a patient experiences a Grade 2 AE that worsens to Grade 3, Grade 3 would be recorded for the entire duration of the event in the eCRF.

9.3.3 Attributing Causality

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

9.4 Handling of Expedited Safety Reports

In accordance with local regulations, the Protocol Chair or designee will notify investigators of all SAEs that are unexpected (i.e., not previously described in the IB), and related to olaparib and IV ascorbic acid. This notification will be in the form of an expedited safety report (ESR) that is to be faxed to the investigators and the study coordinators. Upon receiving such notices, the investigator must review and retain the notice with the IB and where required by local regulations, the investigator will submit the ESR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB institutional guidelines for reporting any other safety information.

9.5 Reporting Adverse Events

9.5.1 Reporting Adverse Events (AEs) and Serious Adverse Events (SAEs)

All AEs (both expected and unexpected) occurring from the first dose of study drug will be captured on the appropriate study-specific case report forms (CRFs).

All AEs experienced by subjects will be collected and reported from the first dose of the investigational agent, throughout the study, and will be followed for 30 days after last dose of study drug unless related to the investigational agent.

All SAEs (including death) occurring from the first dose study drug, throughout the study, and 30 days after the last dose of study drug or before initiation of a new antineoplastic treatment (whichever comes first) must be reported. All SAEs that the investigator considers related to the study drug occurring after the follow-up periods must be reported.

In addition, all SAEs, regardless of causality to study drug and/or administration device, will be reported promptly to the IND sponsor (e-mail: hcao7@jhmi.edu, juram1@jhmi.edu), and kdaughe5@jhmi.edu, within 24 hours of recognition of the event (**Appendix B**). If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

Coordinating Center

The Coordinating Center is the central location for the collection and maintenance of documentation of adverse events and is responsible for submitting adverse event reports to the Protocol Chair promptly. The Coordinating Center will maintain documentation of all adverse event reports for each participating site. Adverse event reports submitted to the Coordinating Center must be signed and dated by the participating site's Principal Investigator. The Coordinating Center will provide appropriate forms to be used by all participating sites for reporting adverse events. Information to be provided must include:

- Subject ID number, and initials
- Date of the event
- Description of the event
- Description of site's response to the event

- Assessment of the subject's condition
- Subject's status on the study (on study, off study, etc.)
- Attribution of event to study drug

Participating Sites

Participating sites are responsible for reporting adverse events to their IRB according to its specific requirements and to the Coordinating Center as follows:

Fatal Events whether anticipated or unanticipated, and whether or not related to the study must be reported to the Coordinating Center within **24 hours** of the participating site Principal Investigator's learning of the event.

Serious and Unanticipated Adverse Events as defined above must be reported to the Coordinating Center within **24 hours** of the participating site Principal Investigator's learning of the event.

Other Serious Adverse Events which may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol must be reported within **three (3) working days** of the participating site Principal Investigator's learning of the event.

Adverse Events which result in no change to protocol, informed consent, or risk to subjects must be reported to the Coordinating Center on a monthly basis.

Adverse event reports are to be faxed to the Coordinating Center at SKCCC. Follow-up reports are faxed, mailed, or sent electronically to the Coordinating Center as necessary.

The investigator must also report follow-up information about SAEs within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within the same time frames described above.

All SAEs must be collected whether or not they are considered causally related to the investigational product. Investigators and other site personnel are responsible for reporting all casually related SAEs to their IRB and the Protocol Chair.

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report the pregnancy of a male patient's female partner within 4 weeks days of completing the trial. All pregnancies of female partners of patients must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as SAEs (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported to the IND sponsor, CRO, McGuff and AZ.

Report AEs to the Protocol Chair and CRO within 24 hours once identified as an unacceptable toxicity (defined in Section 8.1).

Report Olaparib AESIs to Lead Study Coordinator, Protocol Chair, and AstraZeneca within 24 hours once identified (defined in Section 9.1.3) using the form found in Appendix F.

Channing Paller (Protocol Chair): **cpaller1@jhmi.edu**

Harry Cao (Monitor): **hcao7@jhmi.edu**

AstraZeneca: **TrialTCS@astrazeneca.com**
Fax: 302-886-4114

All SAEs (including death) occurring from the first dose study drug, throughout the study, and 30 days after the last dose of study drug or before initiation of a new antineoplastic treatment (whichever comes first) must be reported. All SAEs that the investigator considers related to the study drug occurring after the follow-up periods must be reported.

SAEs will be reported promptly to the Protocol Chair, AstraZeneca, and McGuff within 24 hours of recognition of the adverse event using the form found in **Appendix B**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

SAE reports and any other relevant safety information are to be sent to:

Harry Cao (Monitor): **hcao7@jhmi.edu**

Channing Paller (Protocol Chair): **cpaller1@jhmi.edu**

AstraZeneca: **TrialTCS@astrazeneca.com**
Fax: 302-886-4114

McGuff: **ooviedo@mcguff.com**

9.5.2 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department concerning the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained

- The subject is lost to follow-up
- Death

As soon as relevant information is available, a follow-up SAE report will be submitted to the Protocol Chair, Monitors, AstraZeneca, and McGuff.

9.5.3 Reconciliation of SAEs

The Principal Investigator will reconcile the clinical database SAE cases (case level only) transmitted to Monitors, AstraZeneca (TrialTCS@astrazeneca.com), and McGuff (ooviedo@mcguff.com). Frequency of reconciliation should be approximately every 3 months and prior to the database lock or final data summary. AstraZeneca and McGuff will email, upon request from the Principal Investigator, the reconciliation report. The data elements listed on the AstraZeneca reconciliation report will be used for case identification purposes. If the Principal Investigator determines a case was not transmitted to the Protocol Chair, Monitors , AstraZeneca, and McGuff, the case should be sent immediately to the Protocol Chair, Monitors, AstraZeneca, and McGuff.

9.5.4 Institutional Review Board (IRB)

Participating sites will be responsible for reporting to their IRB. Serious adverse events will be reported to the IRB per institutional standards. Upon receipt, follow-up information will be given to the IRB (as soon as relevant information is available) per institutional standards.

10.0 PHARMACEUTICAL INFORMATION

10.1 Ascorbic Acid

10.1.1 Agent Accountability

The sponsor/investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational products in accordance with the protocol and any applicable laws and regulations.

10.1.2 Mode of Action

Ascorbic Acid (vitamin C) is a water-soluble vitamin. In humans, an exogenous source of ascorbic acid is required for collagen formation and tissue repair. Ascorbic acid is reversibly oxidized to dehydroascorbic acid in the body. These two forms of the vitamin are believed to be important in oxidation-reduction reactions. The vitamin is involved in tyrosine metabolism, conversion of folic acid to folinic acid, carbohydrate metabolism, synthesis of lipids and proteins, iron metabolism, resistance to infections, and cellular respiration.

10.1.3 Description

Ascor L 500® (Ascorbic Acid Injection, USP) 500mg/mL, is available in a 50-mL sterile dispensing vial. Ascorbic Acid injection is a clear, colorless to slightly yellow sterile, solution of Ascorbic Acid in Water for injection.

10.1.4 Preparation
When dispensing vials, use aseptic technique. Dispense entire contents in aliquots under a laminar flow hood without delay. Prepare stoppers with a suitable antiseptic technique. Do not use unless solution is clear and seal is intact. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit. Ascorbic acid should be diluted in sterile water for injection (final volume of 1000ml).

The ascorbic acid for infusions will be prepared by the pharmacy. The calculated dose of ascorbic acid will be diluted in Sterile Water for injection USP.

A study-specific worksheet will be completed when preparing ascorbic acid infusions. The worksheet will document the dose prepared and calculations for dose preparation.

10.1.5 Storage
Store between 2°- 8°C. Do not freeze.

10.1.6 Stability
The administration of ascorbic acid infusion must be completed within 72 hours of preparation. If not used immediately, the infusion solution must be refrigerated while also protected from light to keep the product stable. The maximum 72-hour period under refrigeration and protected light conditions includes the product administration period.

10.1.7 Route of Administration
Ascorbic acid should be administered by intravenous infusion. For intravenous injection, dilution into a large volume parenteral of water is recommended to minimize the adverse reactions associated with intravenous injection. Infusion will be administered at 0.75-1 gram per minute not to exceed 500 mL per hour. Ports are recommended but not mandatory due to frequency of infusion.

10.1.8 Patient Care Implications
Too rapid intravenous administration of the solution may cause temporary faintness or dizziness. Expected adverse events and potential risks are described in **Section 7.9.** Appropriate dose modifications are described in **Section 8.2.** No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Diabetics, patients prone to recurrent renal calculi, those undergoing stool occult blood tests, and those on sodium-restricted diets or warfarin anticoagulant therapy[35,36] should not take excessive doses of ascorbic acid over an extended period of time. Diabetics taking more than 500 mg of ascorbic acid daily may obtain false readings of their urinary glucose test. No exogenous ascorbic acid should be ingested for 48 to 72 hours before amine dependent stool occult blood tests are conducted because possible false-negative results may occur. Heparin, enoxaparin, aspirin, NSAIDS, or other anticoagulant therapies are allowed.

Ascorbic acid at pharmacologic doses can give false positive results for blood glucose with some commercial point of care glucometers (glucose meters), although this has not been seen with clinical chemistry laboratory autoanalyzers. Glucometers should not be used to measure blood glucose during and up to 10 hours after intravenous ascorbate administration[56,57]. Patients should be counseled that correction of falsely high blood glucose levels with excess insulin may cause hypoglycemia and death, that some strips provide false readings while others, such as Bayer Contour are less likely to do so. They should also be counseled that if they do see high blood glucose readings following IV ascorbic acid, they should not increase their insulin unless the high glucose reading is confirmed at least 10 hours after IF AA administration.

10.1.9 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational products will be destroyed at the site per institutional standards.

10.2 Olaparib

10.2.1 Agent Accountability

The sponsor/investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational products in accordance with the protocol and any applicable laws and regulations.

10.2.2 Mode of Action

The mechanism of action for olaparib activity as a single agent has been proposed to involve the trapping of inactivated PARP onto the single-strand breaks preventing their repair and generating a potential block for cellular DNA replication.[6,7] An important consequence of this is that processing of trapped PARP-DNA complexes and/or the stalling of replication forks, or collapsing of replication forks, is predicted to lead to the generation of the more serious DNA DSBs.[6,7]

10.2.3 Description

Olaparib is available as 150 mg and 100 mg tablets.

- 150 mg tablets: green to green/grey, oval, bi-convex, film-coated tablet, with debossment ‘OP150’ on one side and plain on the reverse, are available in:
    - Bottles of 60 tablets (NDC 0310-0679-60) and
    - Bottles of 120 tablets (NDC 0310-0679-12).
- 100 mg tablets: yellow to dark yellow, oval, bi-convex, film-coated tablet, with debossment ‘OP100’on one side and plain on the reverse, are available in:
    - Bottles of 60 tablets (NDC 0310-0668-60) and
    - Bottles of 120 tablets (NDC 0310-0668-12)

10.2.4 Preparation
Olaparib is presented for oral administration as a green, film-coated tablet containing 100 mg or 150 mg of drug substance. The 100 mg strength is also available as a yellow, film-coated tablet. Olaparib tablets are supplied in high-density polyethylene (HDPE) bottles containing desiccant. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence.

Dosing containers will be supplied to contain sufficient medication for at least 28 days plus coverage, 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.

10.2.5 Storage
Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store in original bottle to protect from moisture.

10.2.6 Route of Administration
Olaparib will be administered orally every 12 hours without regard to food at the dose specified. 100mg and 150mg tablets will be supplied.

10.2.7 Patient Care Implications
Expected adverse events and potential risks are described in **Section 7.9.** Appropriate dose modifications are described in **Section 8.2.** No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.
If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not taken and the patient should take their allotted dose at the next scheduled time.

10.2.8 Returns and Reconciliation
The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational products will be destroyed at the site per institutional standards.

11.0 CORRELATIVE/SPECIAL STUDIES
Complete instructions for the collection, processing, and shipment of correlative samples will be provided in a separate laboratory manual. All specimens should be correctly labeled with patient initials, study-specific ID number, protocol number, and date of collection.

11.1 Tumor Tissue Studies

Tumor tissue samples will be submitted for whole exome sequencing to identify mutations (or liquid biopsy prior to study entry). Detailed instructions for tissue collection, processing and shipment are provided in the laboratory manual. FFPE block and 1 H&E side will be sent to Matt Schiewer lab for processing. Tumor tissue on slides are optimally 25mm^2 in area and 4-5 microns thick. For optional on study biopsy see γH2AX discussion (Section 11.2.2).

11.2 Peripheral Blood Studies

Blood for measuring circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and γH2AX in CTCS at C1D1 (pre-infusion), C1D8 (pre-infusion), 4 weeks (C2D1) post infusion, 12 weeks (C4D1) post infusion, and at EOT – see study calendar for details. Baseline sample at screening should be collected before patient receives study drug. Complete instructions for the collection, processing, and shipment of samples will be provided in a separate lab manual.

11.2.1 Circulating tumor DNA (ctDNA)

Circulating tumor DNA (ctDNA) can be found in the blood of cancer patients[37], including prostate cancer patients[38], as part of "liquid biopsy" efforts. There is evidence that ctDNA has value in diagnosis and/or therapeutic applications[39], including in guiding use of PARP inhibitors in prostate cancer.[40]

Baseline, 4 week, 12 week, and progression plasma samples will be collected in order to evaluate the mutational patters as a function of therapeutic intervention, with the potential to identify new mutations after treatment. Plasma will be obtained by phlebotomy. Blood will be collected in tubes provided in kits supplied by Foundation Medicine. Tubes of 10ml of whole blood are optimally collected for this assay. Collected specimens can be stored at room temperature in the collection tubes and sent via overnight shipment to the processing laboratory.

It was recently reported that a Phase II trial (NCT01485861)[41] of mCRPC patients treated with abiraterone +/- ipatasertib demonstrated that "*Baseline (BL) ctDNA positively correlated with radiological progression-free survival (fPDS; HR: 1.8 [95% CI 1.3-2.6], p < 0.01); this association with rPFS was maintained in a multivariate cox model with >5 baseline clinical variables (HR: 1.6 [95% CI 1.1-2.4], p=0.011). Patients with a C3D1 reduction in ctDNA had superior rPFS compared to patients with a C3D1 increase in ctDNA (HR: 2 [95% CI 1.3-3.2]; p < 0.01). The rate of ctDNA clearance at C3D1 was higher with Ipastasertib 400mg arm compared to placebo (56.3% versus 24.4%, p < 0.1). We find that changes in ctDNA associated with best confirmed overall response (p=0.024); CR patients had greatest reduction in ctDNA (mean of -23.4%), followed by PR (-16.3%), then SD (-4.1%), and lastly PD patients (-1.3%). Changes in ctDNA levels correlated with SLD changes (rs = 0.289, p = 0.05) and also PSA changes (rs = 0.33, p < 0.01). Changes in ctDNA were associated with rPFS in a multivariate cox analysis that included PSA change (p < 0.01), as well as in a separate multivariate analysis that included SLD change (p < 0.01).*"[41]

We hypothesize that we will be able to retrospectively predict which patients will respond to the combination of ascorbate and olaparib. This will be useful in the

assessment of treatment response, including correlation with rPFS, and will potentially identify mechanisms of resistance.

11.2.2 γH2AX foci in CTCs and/or FFPE biopsy tissues

Given that pharmacological ascorbate generates ROS which in turn elicits DNA double-strand breaks, and that PARP inhibition leads to diminished capacity to repair DNA damage, an exploratory endpoint to this study will be to evaluate DNA double-strand breaks via immunostaining for γH2AX foci in CTCs and optional FFPE biopsy tissues. The extent of DNA damage as determined by γH2AX foci will be correlated with patient response.

Additionally, given that olaparib targets PARP activity, the impact of the combination of pharmacological ascorbate and olaparib on PARP activity will be evaluated as an exploratory endpoint of this study via immunostaining for PAR (the enzymatic output of PARP activity) in CTCs and optional FFPE biopsy tissues. The extended PARP activity as determined by PAR staining will be correlated with patient response. https://www.embopress.org/doi/pdf/10.15252/emmm.201708816

11.3 Urine Studies

Urine for measuring F2-Isoprostanes and 8-OHdG (markers of oxidative stress) will be collected at Screening, 4 weeks (C2D1), 12 weeks (C4D1), and at EOT - see study calendar for details. Baseline sample at screening should be collected before patient receives study drug. Complete instructions for the collection, processing, and shipment of samples will be provided in a separate lab manual.

11.3.1 8-oxo-2'-deoxyguanosine

8-hydrozy-2'deoxyguanosine is a form of damaged DNA caused by excess free radicals and is a marker of DNA oxidation which can be measured in the urine.[44] At baseline, men with prostate cancer have an intermediate level of 8-OH-dG detected in urine, which has transiently increased after radiation therapy in a small study of seven men.[45] Urinary levels were shown to be decreased in men who were treated in a trial of antioxidants with selenium-enriched yeast.[46] Serum levels were shown in one study of 32 men with localized prostate cancer to be decreased following dietary intervention with lycopene.[47] Prostatic tissue levels of 8-OHdG were not significantly decreased in a neo-adjuvant trial of 70 men randomized to pomegranate extract or placebo.[48] In our population, we hypothesize 8-OHdG will be increased after being treated with the study intervention, and will correlate with response to treatment.

11.3.2 F2-Isoprostanes

F2-Isoprostanes are prostaglandin like compounds that are produced by the peroxidation of arachidonic acid, which is catalyzed by free radicals and is independent of cyclooxygenase.[49] Urinary measurement gives an accurate measure of in vivo oxidative stress and is considered to be one of the most reliable biomarkers of oxidative stress.[50] Within men with prostate cancer, there have been

cross-sectional associations with lower levels of 8-isoprostane with higher antioxidant intake.[51] The data is mixed on association of isoprostanes and incident prostate cancer with some studies showing a positive association with F2-isoprostane level and risk of incident prostate cancer[52,53] and others showing no association with urinary F2-isoprostanes and incident prostate cancer.[54,55] However, the literature suggests this is the most reliable biomarker[50] and warrants further study in our prostate cancer patients.

11.4 Genomic Analysis

Prior genomic sequencing will be collected to document any mutations that are germline or somatic.

12.0 DATA REPORTING/REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in **Section 9.0**.

12.1 Data Management

All information will be collected on study-specific case report forms (CRFs) in RedCap by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator.

CRFs will be used to capture study results and data. The study coordinator or other authorized study personnel will transcribe data from source documents onto paper or eCRFs. Before or between visits, the Protocol Chair (or designee) may request copies of the CRFs for preliminary medical review. Once the CRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF.

<u>Protocol Chair</u>

The Protocol Chair and/or designee 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 SAE
- Reviewing data from all sites.

<u>Coordinating Center (Johns Hopkins University)</u>

The Coordinating Center (or its representative) is responsible for performing the following tasks:

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

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

Participating 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 Coordinating Center.
- Consent subjects promptly and randomize eligible subjects in EDC.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.
- Comply with auditing and monitoring requests

12.2 Safety Meetings

Scheduled meetings will take place weekly, biweekly or monthly depending on patient enrollment, and will include the protocol principal investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

Monthly teleconferences will be scheduled to include the Coordinating Center and the clinical trial sites. During these meetings, the Coordinating Center and clinical trial sites shall discuss the following: study protocol updates, safety data, enrollment status, and progress of data for objectives.

12.3 Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring 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. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. Eligibility for all sites will be monitored by the Protocol Chair or authorized representatives of the Coordinating Center. The protocol will be internally monitored by the Principal Investigator at each site. The PI shall internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation. Protocol Chair is ultimately responsible for external monitoring of the trial. External monitoring will occur according to the following guidelines:

Participating Site(s): The protocol will be monitored by authorized representatives of the Coordinating Center.

Authorized representatives of the Coordinating Center will conduct remote monitoring of satellite sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP).

12.4 Populations of Interest

The safety population includes all subjects who received at least one dose of olaparib and IV ascorbic acid study treatment. The safety population will be conducted on the basis of the actual treatment received. All safety outcomes will be assessed using the safety population for analysis.

12.5 Study Documentation

12.5.1 Informed Consent and Authorization for use and Disclosure of Protected Health Information

Written informed consent and authorization of use and disclosure of protected health information (PHI) must be obtained from each subject (or the subject's legally authorized representative) before performing any study-specific screening/baseline period evaluations. One copy of the signed informed consent form (ICF) and authorization for use and disclosure of the PHI form will be given to the subject and the investigator will retain the original. The ICF and authorization for use and disclosure of PHI, which is prepared by the investigator or the site, must be reviewed and approved by the Protocol Chair, the study monitor (if applicable) and the site's IRB before the initiation of the study. The ICF must contain the 20 elements of informed consent described in ICH E6, Section 4.8. The authorization for use and disclosure of PHI must contain the elements required by Title 45 of the Code of Federal Regulations (CFR), Section 164.508(b), for valid authorizations.

12.5.2 Investigator Study Files

Documentation about the investigator and study staff, the IRB and the institution, is required before study site initiation. A list of required documents will be provided by the Protocol Chair or designee to each participating investigator. Copies of these documents as well as supplemental information, such as the investigator's obligations, IB, clinical study protocol and amendments, safety information, investigational agent information, biological samples and laboratory procedures, SRM, study logs and Protocol Chair/investigator/study monitor correspondence will be kept on-site in study site-specific files.

The Protocol Chair or designee will be responsible for maintaining original and backup of all CRF data. The investigator is responsible for maintaining backup of all electronic data systems used for primary documentation or source documentation. Backup of electronic data will be performed periodically as described in the site-specific SOPs. Backup records must be stored at a secure location on site and backup and recovery logs must be maintained to facilitate data recovery. If an electronic

medical records system that is not supported by the Protocol Chair or designee (or is discontinued or decommissioned) is used, the investigator must maintain a system to retrieve these records or arrange for the transfer of these records to an alternate electronic format or to paper.

Changes to any electronic records require an audit trail, in accordance with 21 CFR 11.10(e), and should include who made the changes and when and why the changes were made. An audit trail is defined as a secure, computer-generated, time-stamped electronic record that will allow reconstruction of the course of events relating to the creation, modification and deletion of an electronic record. Audit trails must be created incrementally, in chronological order and in a manner that does not allow new audit trail information to overwrite existing data. Audit trails should be in a readable format and readily available at the study site and any other location where electronic study records are maintained.

Audit trails are generated automatically for eCRFs. The investigator is responsible for maintaining audit trails of all electronic data systems used for primary documentation or source documentation.

12.5.3 Case Report Forms and Source Documentation

The investigator must make study data accessible to the site monitor, to other authorized representatives of the Protocol Chair (or designee) and to the appropriate regulatory authority inspectors. The original CRF for each subject will be checked against source documents at the study site by the site monitor.

12.5.4 Retention of Study Documents

According to ICH E6, Section 4.9, all CRFs, as well as supporting paper and electronic documentation and administrative records, must be retained for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of an individual product. Longer retention periods may apply. The Protocol Chair will notify investigators as to when documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written approval from the Protocol Chair. If the investigator relocates, retires or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator at the institution where the study was conducted.

Audit trails for electronic documents must be retained for a period at least as long as that required for the subject electronic records to which they pertain. The investigator must retain either the original or a certified copy of audit trails.

12.5.5 Data Confidentiality and Subject Anonymity

All information about the nature of the proposed investigation provided by the Protocol Chair or their representative to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject or the appropriate regulatory authority) must be kept in confidence by the investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents retrieved from the site or sent to the Protocol Chair, AstraZeneca, McGuff, regulatory agencies, or central laboratories/reviewers. Documents that identify the subject (e.g., the signed ICF) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the study monitor, Protocol Chair or their representative.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This pilot trial has an exact single-stage design.[58] It will evaluate olaparib and IV ascorbate in patients with metastatic castration resistant prostate cancer in which a DNA repair mutation is absent. The hypothesis of the study is that olaparib will synergize with IV ascorbic acid to improve clinical outcomes in this population.

Primary objective: To estimate the proportion of patients with metastatic castration resistant prostate cancer (mCRPC) having a 50% reduction in PSA from baseline (PSA50 response).

Secondary objectives:

1) To evaluate the safety and tolerability of olaparib in combination with IV ascorbic acid in patients with mCRPC.
2) To estimate the median radiographic progression free survival (rPFS) of patients with mCRPC receiving olaparib in combination with IV ascorbic acid
3) To estimate the median time to PSA doubling from baseline of patients with mCRPC receiving olaparib in combination with IV ascorbic acid.
4) To estimate the median PSA progression free survival (PSA PFS) of patients with mCRPC receiving olaparib in combination with IV. ascorbic acid
5) To assess overall survival (OS) in patients with castration resistant prostate cancer.

Exploratory objectives: Examine correlates that may be predictive of the clinical outcomes: PSA_{50} response and rPFS

1) To quantify ctDNA and perform mutational analysis in the peripheral blood and compare it to any baseline germline or somatic mutations (document prestudy on case report form)
2) To quantify circulating tumor cells (CTCs) in the peripheral blood at baseline, 4 weeks, 12 weeks, and upon progression and assess γH2AX foci in CTCs
3) Optional γH2AX foci FFPE biopsy tissues
4) To measure F2-isoprostanes in the urine as a pharmacodynamic measure of oxidant injury at baseline, 4 weeks, 12 weeks, and upon progression.
5) To measure 8-oxo-2'-deoxyguanosine as a measure of oxidative stress in the urine at baseline, 4 weeks, 12 weeks, and upon progression.

13.2 Primary Endpoint Definition

The primary endpoint in this study is based on PSA_{50} response. PSA_{50} response will be 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. PSA values will be measured monthly during the trial.

13.3 Secondary Endpoint Definitions

- Safety and tolerability will be defined by frequency of the drug-related adverse events by grade as assessed by the NCI CTCAE Version 5.0, lab measurements, and vital signs.
- Radiographic progression will be defined as soft tissue disease progression by modified RECIST criteria 1.1 (baseline LN size must be >1.0 cm to be considered target or evaluable lesion) or by development of two or more new bone lesions not consistent with tumor flair for prostate cancer working group 3. Radiographic progression free survival (rPFS) is defined as the number of months from initiation of therapy to date of first radiographic progression, death from any cause, or last patient evaluation. Patients who have not progressed or died will be censored at the last date they were assessed and deemed progression-free.
- Time to PSA doubling from baseline is a time-to-event outcome. Time is measured from the initiation of therapy until the PSA has increased to 200% of baseline value, and confirmed with another measurement at least 4 weeks later, or death. The date of PSA doubling will be the first value recorded (not the confirmatory value).
- PSA PFS is defined as time to first PSA failure (two consecutive increases in PSA of 50% and ≥5 ng/mL above nadir) or death.
- OS is defined as the number of months from initiation of therapy to death due to any cause.

13.4 Correlative Endpoint Definitions

- Circulating tumor DNA (ctDNA) will be measured in peripheral blood to evaluate changes in mutation patterns, which will be correlated to therapeutic outcomes and compare to any prior noted mutations in germline or somatic sequencing
- γH2AX foci in CTCs and optional FFPE biopsy tissue
- F2-isoprostane levels will be evaluated in urine as a measure of oxidative injury and will be correlated to therapeutic outcomes and toxicities.
- 8-oxo-2'-deoxyguanosine will be evaluated in urine as a measure of oxidative stress and correlated to therapeutic outcomes.

13.5 Sample Size/Accrual Rate

Accrual to this study is expected to be one patient per month. For this combination to be considered for further study a PSA_{50} response of 23% or more would be desirable. Our null hypothesis of 3% is based on the low PSA_{50} response rate, 3% (1 of 33), reported by Mateo et al.[22] for this patient population. This single-stage design has a 95% chance (α = 0.05) of rejecting the therapy if the true percentage of patients with some benefit from treatment is less than or equal to 3% and an 80% chance of concluding the therapy is beneficial if the true percentage is 23% or more. Twelve patients, will be assessed for 6 months and if 2 or more achieve a PSA_{50} response, the therapy will be considered for a larger study. Patients enrolled who never receive any study related therapy will be

replaced. Enrollment would be allowed to continue, up to a maximum of 15 patients, to replace those patients that drop-out early.

13.6 Futility and Safety Monitoring Plan

Given the small number of patients and the importance of obtaining correlative data to consider during the final evaluation of the study results, there will be no futility monitoring for efficacy during this pilot study. The trial will however employ a standard safety monitoring plan for adverse events. In addition, if any patient is diagnosed with an adverse event of special interest: myelodysplastic syndrome, acute myeloid leukemia, new primary malignancy (other than MDS/AML) or pneumonitis during the trial, the trial will be paused for a safety review.

Toxicity will be monitored continuously for grade 3-4 adverse events that do not resolve to grade 2 following four-weeks drug discontinuation (per section 8.1). The stopping rule is based on the posterior probability that the combination of treatments is too toxic. If the rate of these toxicities convincingly exceeds 30%, the study PI will hold enrollment if the posterior probability of risk greater than 0.30 is 65% or higher. The prior for this toxicity monitoring rule is beta (2,6). This corresponds to assuming our prior guess for the toxicity rate is 25%, and there is 90% probability that this proportion is between 5% and 52%.

Table 9. Monitoring rule for safety.

Stop if safety events are seen	2	3	4	5
in N patients	2	3-6	7-9	10-12

The operating characteristics of the stopping rule shows the percent of the time that the monitoring rule would pause the study under different hypothetical risks of toxicity, along with the average sample size (based on 5000 simulations).

Table 10. Operating Characteristics for Safety

Risk of safety event	0.15	0.25	0.30	0.35	0.40	0.45	0.50
% of Time Study Stops	7.4%	26.5%	39.8%	52.3%	67.8%	78.6%	86.3%
Expected Sample Size	11.5	10.4	9.6	8.7	7.7	6.9	6.1

13.7 Analysis of Primary Endpoint

The primary endpoint is based on PSA_{50} response. All patients who receive at least one dose of olaparib and IV ascorbic acid will be evaluable for the primary objective. If patients do not have adequate PSA data after the initiation of therapy due to stopping for toxicity or withdrawing consent, then they will be considered unevaluable. The PSA_{50} response will be calculated as a proportion with 90% confidence intervals.

PSA_{50} response will be defined as a decrease in the PSA to 50% less than the baseline PSA upon enrollment in the trial. Patients must receive at least one dose of olaparib and IV ascorbic acid to be considered evaluable. After the initial measurement showing a >50% decrease in PSA compared to baseline, a second measurement must confirm the decrease,

and the measurements must be at least 4 weeks apart. PSA_{50} response rate will be calculated as a proportion with 90% confidence intervals.

13.8 Analysis of Secondary Endpoints

The **safety analysis** will be performed in all subjects receiving combination olaparib and IV ascorbic acid. AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE (based on preferred terminology defined by Medical Dictionary for Regulatory Activities (MedDRA; Version 13.1, or later) will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. If 2 or more AEs are reported as a unit, the individual terms will be reported as separate experiences. Changes in vital signs, hematology and clinical chemistry parameters from baseline to the end of the study will be examined. Toxicity will be tabulated by type and grade. Toxicities will be characterized according to the CTCAE version 5.0 Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

Radiographic progression-free survival (**rPFS**) is defined as the number of months from initiation of therapy (cycle 1, day 1) to date of first radiographic progression, death from any cause, or last patient evaluation. Patients must receive at least one dose of olaparib and IV ascorbic acid to be considered evaluable. Radiographic progression will be determined by modified RECIST criteria 1.1 by development of two or more new bone lesions not consistent with tumor flair for prostate cancer working group 2. Patients who have not progressed or died will be censored at the last date they were assessed and deemed progression-free. rPFS will be summarized and six month estimates for rPFS will be reported using the Kaplan-Meier method with 90% confidence intervals.

PSA doubling time from baseline is a time-to-event outcome. Time in months is measured from the initiation of therapy (cycle 1, day 1) until the PSA has increased to 200% of baseline value after a minimum of 12 weeks of therapy and has been confirmed with another measurement at least 4 weeks later, or death. The date of PSA doubling will be the first value recorded (not the confirmatory value). Patients must receive at least one dose of olaparib and IV ascorbic acid to be considered evaluable. PSA doubling time will be summarized using the Kaplan-Meier method with 90% confidence intervals.

Prostate-specific antigen progression-free survival (**PSA PFS**) is defined as the number of months from initiation of therapy (cycle 1, day 1) to first PSA failure (two consecutive increases in PSA of 50% at least 4 weeks apart and ≥5 ng/mL above nadir) or death. Patients must receive at least one dose of olaparib and IV ascorbic acid to be considered evaluable. Patients who do not experience PSA failure or die will be censored at the last date of PSA measurement. PSA PFS will be summarized using the Kaplan-Meier method with 90% confidence intervals.

OS is defined as the number of months from the initiation of therapy to death due to any cause. Patients who are alive or lost to follow up as of the data analysis cutoff date will be

censored at the last date they were assessed. OS will be summarized using the Kaplan Meier method with 90% confidence intervals.

13.9 Exploratory/Correlative Analysis

The additional correlative analyses will be primarily descriptive in nature. Plots (e.g. histograms, scatter and spaghetti plots) and summary statistics (medians, ranges, counts, proportions) will be used to summarize patterns over time and compare outcomes. Comparisons in the pre- and post-treatment responses will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and McNemar's tests for dichotomous or categorical variables. Peripheral blood samples will be analyzed for ctDNA, CTCs and γH2AX foci in CTCs at serial time points during the study in order to identify therapeutic targets, biomarkers, and predictors of response. Additionally, urine samples will be analyzed for F2-isoprostane and 8-oxo-2'-deoxyguanosine levels at serial time points during the study in order to identify the impact of study therapy on oxidative toxicities, which will be correlated to therapeutic outcomes.

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, microbial sequencing, neoepitope prediction, mutation burden, and bioinformatic analysis will be performed either at an on-campus laboratory or at an off-campus sequencing service. All the samples will be de-identified before sending to any laboratory for sequencing. The FASTQ files, BAM files and VCF files will be generated and analyzed. Genomic sequencing data will be stored and computations conducted using a JH IT managed subscription of Azure.

Results from the sequencing studies will not be released to the patients. These studies are for research purposes only and are not using a clinically validated platform

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APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease 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 (e.g., 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 of his/her 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 more than 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: Serious Adverse Event Reporting Form

Please notify: Channing Paller, MD within 24 hours (email: cpaller1@jhmi.edu)
Monitor/Harry Cao within 24 hours
(emails: hcao7@jhmi.edu, kdaughe5@jhmi.edu)
AstraZeneca within 24 hours (email: TrialTCS@astrazeneca.com; fax: 302-886-4114)
McGuff within 24 hours (email: ooviedo@mcguff.com

<table>
<tr><td>Protocol Title:</td><td colspan="3">Phase II Study of PARP Inhibitor Olaparib and IV Ascorbate in Metastatic Castration Resistant Prostate Cancer</td></tr>
<tr><td>Protocol Number:</td><td>Signature of PI:</td><td>Principal Investigator:
Dr. Channing Paller</td><td>Date of Report:</td></tr>
<tr><td rowspan="2">Report Type:
☐Initial
☐Follow-up
☐Final Follow-up
☐Death
☐Addendum to:</td><td rowspan="2">Serious Criteria (check all that apply):
☐Death
☐Life-threatening
☐ Hospitalization or Elongation of Existing Hospitalization
☐ Other Important Medical Event
☐ Cancer
☐ Overdose
☐ Other:_____</td><td>Hospital Admission Date:</td><td>Date Event Discovered:</td></tr>
<tr><td>Hospital Discharge Date:</td><td>SAE ID:</td></tr>
<tr><td colspan="4">Section A: Subject Information</td></tr>
<tr><td colspan="2">Subject ID:</td><td>Subject Gender:
☐Male
☐Female</td><td>Subject Age:</td></tr>
<tr><td colspan="4">Section B: Event Information</td></tr>
<tr><td>Event diagnosis or symptoms:</td><td>Event Grade:</td><td>Cause of death (if applicable):</td><td>Event Outcome:
☐ Not Recovered
☐ Recovering
☐ Recovered
☐ Recovered with sequelae
☐ Death
☐ Unknown</td></tr>
<tr><td colspan="2">Event Onset Date (or Date of Death):</td><td colspan="2">Event End Date:</td></tr>
<tr><td colspan="4">Section C: Study Drug Information</td></tr>
<tr><td colspan="4">Investigational Product:
Olaparib 300 mg BID
IV Ascorbic Acid (1 g/kg, 2x per week)
Indication: Castration Resistant Prostate Cancer (CRPC)</td></tr>
</table>

Number of Total Cycles:	**Action taken with the study drug:** ☐ None ☐ Interrupted ☐ Delayed ☐ Discontinued

Date of First Dose:	**Date of Last Dose prior to Event:**	

Relationship to:	**Olaparib**	**IV Ascorbic Acid**	**Underlying Disease**
Unrelated	☐	☐	☐
Related	☐	☐	☐

Section D: Brief Description of the Event:

Section E: Relevant Tests/Laboratory Data

Section F: Relevant Medical History

Section G: Concomitant Drug (Not related to SAE)

Name of the Drug	**Start Date**	**Stop Date**	**Route**	**Dose**	**Frequency**

Section H: Comments
Additional Documents: ☐ Please specify

APPENDIX C: Contraception

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 three months after the last dose for male patients. Periodic abstinence (e.g. calendar ovulation, sympothermal, 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 D: 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 and McGuff 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) $\geq$ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) $\geq$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 $\geq$ 3x ULN and TBL $\geq$2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g. elevated ALP indicating cholestasis, viral hepatitis, another drug.
- The elevations do not have to occur at the same time or within a specified 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 $\geq$ 3xULN
- AST $\geq$ 3xULN
- TBL $\geq$ 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 guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met:

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

- Notify the AstraZeneca and McGuff 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 are 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 below 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 an 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 assessed 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 when 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

APPENDIX E: Modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1 will be used in this study for assessment of tumor response. While either CT or MRI may be used utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

The RECIST 1.1 criteria have been modified specifically for this study so a lymph node will be considered pathological if it measures >20 mm in the short axis as opposed to the standard >15 mm cut off.

Disease Parameters

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

> Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable unless there is evidence of progression in the irradiated site. Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥20 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <20 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline

sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

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

For Subjects with Measurable Disease (i.e., Target Disease)

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

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

** Only for non-randomized trials with response as primary endpoint.

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

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

Reference

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX F: Adverse Event of Special Interest Reporting Form

Please notify: Channing Paller, MD within 24 hours (email: cpaller1@jhmi.edu)
Monitor/Harry Cao within 24 hours
(emails: hcao7@jhmi.edu, kdaughe5@jhmi.edu)
AstraZeneca within 24 hours (email: TrialTCS@astrazeneca.com; fax: 302-886-4114)
McGuff within 24 hours (email: ooviedo@mcguff.com)

Protocol Title:	**Phase II Study of PARP Inhibitor Olaparib and IV Ascorbate in Metastatic Castration Resistant Prostate Cancer**		
Protocol Number:	**Signature of PI:**	**Principal Investigator:**	**Date of Report:**
Report Type: ☐ Initial ☐ Follow-up ☐ Final Follow-up ☐ Addendum to:	**Event Onset Date:**	**Event End Date:**	**Date Event Discovered:**
Section A: Subject Information			
Subject ID:	**Subject Gender:** ☐ Male ☐ Female	**Subject Age:**	
Section B: Event Information			
Event diagnosis or symptoms:	**Event Grade:**	**Event Outcome:** ☐ Not Recovered ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Death ☐ Unknown	
Section C: Study Drug Information			
Investigational Product: Olaparib 300 mg BID IV Ascorbic Acid (1 g/kg, 2x per week) **Indication:** Castration Resistant Prostate Cancer (CRPC)			
Number of Total Cycles:	**Action taken with the study drug:** ☐ None		

Date of First Dose:	**Date of Last Dose prior to Event:**	☐ Interrupted ☐ Delayed ☐ Discontinued Drug(s) discontinued:

Relationship to:	**Olaparib**	**IV Ascorbic Acid**	**Underlying Disease**
Unrelated	☐	☐	☐
Related	☐	☐	☐

Section D: Brief Description of the Event:

Section E: Relevant Tests/Laboratory Data

Section F: Relevant Medical History

Section G: Concomitant Drug (Not related to SAE)

Name of the Drug	**Start Date**	**Stop Date**	**Route**	**Dose**	**Frequency**

Section H: Comments

Additional Documents: ☐ Please specify