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Open-Label, Pilot Study of Olaparib as a Neoadjuvant Therapy for Patients Undergoing Prostatectomy for Localized Prostate Cancer

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
BRCA1	Breast Cancer Susceptibility Gene 1
BRCA2	Breast Cancer Susceptibility Gene 2
CFR	Code of Federal Regulations
CT	Computerized Tomography
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HRD	Homologous Recombination Deficiency
IRB	Institutional Review Board
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of Mercury
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)]
PARPi	PARP inhibitor
pCR	Pathological Complete Remission
PSA	Prostate-Specific Antigen
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-Life
US	United States
WBC	White Blood Cell Count

1. INTRODUCTION

This is a pilot open-label study designed to assess the pathological complete response rate following 3 months of neoadjuvant therapy with olaparib in patients with germline or somatic DNA repair deficiency with localized prostate cancer for whom radical prostatectomy is indicated.

1.1 Background

Prostate cancer is the most common cancer of men and among the most lethal, with an estimated 26,000 men per year dying of prostate cancer anticipated in 2017. [1] Surgery, radiation, and androgen deprivation therapy (ADT) have been standard therapies for locally advanced prostate cancer. The principal reason for progression after primary therapy is systemic micrometastases, which are not adequately addressed at the time of local treatment. The determinants of lethality at the time of diagnosis of prostate cancer have been poorly defined.

Homologous Recombination Deficiency (HRD) in prostate cancer - Metastatic prostate cancer is enriched in pathogenic inactivation of homologous recombination (HR) genes such as BRCA2 and ATM (20-25% of metastatic castration resistant prostate cancer (mCRPC)) as defined in the PCF/SU2C biopsy study of mCRPC [2]. Approximately half of the HR deficient (HRD) tumors (12% of all mCRPC patients) have a pathogenic germline variant in HR genes which is part of the mechanism of inactivation. The University of Washington/Fred Hutchinson Cancer Research Center was the leading clinical site in both efforts and the lead group in the work defining germline deficiencies in men with metastatic prostate cancer [2,3]. The enrichment in patients with an inherited, germline HR deficiency presumably results from the aggressiveness of these tumors which has been demonstrated in BRCA2 mutated localized prostate cancer [4-6]. Men who are carriers of pathogenic germline BRCA variants diagnosed with prostate cancer carry an 8 fold higher risk of prostate cancer specific death than unselected men with prostate cancer when unadjusted for other risks. Carrier men with metastatic prostate cancer had a shorter survival than unselected men with metastatic prostate cancer, implying that these cancers develop resistance to androgen deprivation and subsequent therapies more rapidly and are less dependent on androgen receptor signaling than non-mutated cancers. Men with intermediate/high risk localized prostate cancer in The Cancer Genome Atlas study (TCGA) demonstrated a 4.6% frequency of pathogenic germline HRD variants [7]. The presence of germline HRD is well known to increase the risk of malignancy, particularly in women who carry BRCA variants [8]. In the vast majority of carrier women who develop breast or ovarian cancer, both BRCA alleles are inactive due to either copy loss or a second mutational event in the other allele resulting a loss of DNA repair capacity in tumor, which is greater than that of normal tissue, in which only one allele is inactivated[9,10].

Activity of Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors in HRD cancer – DNA repair is critical to maintenance of cellular function and a primary mechanism of preventing carcinogenesis. Multiple pathways to repair DNA have evolved, including base excision repair and homologous recombination, among others [11].

DNA repair relies on sensing of DNA damage, excision and repair. The pathway which repairs the lesions with the most carcinogenic potential, double strand breaks, with the greatest fidelity is the homologous recombination (HR) pathway. 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 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, PARP inhibition may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens. BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models *in vivo* [12,13] and in the clinic [14]. Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents. The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair [15,16]. Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies

Clinical experience in the treatment of breast ovarian and prostate cancer. In epithelial ovarian cancer, the use of olaparib as maintenance therapy after chemotherapy provided significant improvements in progression free and overall survival in patients with germline BRCA mutations and led to FDA approval of olaparib[17,18]. A second PARP inhibitor, rucaparib, was recently FDA approved for the treatment of ovarian cancer in BRCA carriers because of significant improvements in progression free survival compared to historical comparisons [19]. The data for activity of olaparib in prostate cancer comes from an initial study of olaparib in an unselected cohort of men with heavily pretreated metastatic, castration resistant prostate cancer. In this study 16 of 50 patients responded and 14 of those tumors contained an inactivating HR mutation in the tumor, providing a potential predictive biomarker [20]. A range of mutations were found to be sensitive, including BRCA, PALB2, ATM, FANCA and CHEK2. The response rate in patients whose tumors contained HRD was 88%. All 7 patients with BRCA2 loss (4 with biallelic somatic loss, and 3 with germline mutations) and 4 of 5 with ATM aberrations responded. This remarkably high response rate in a heavily pretreated population with prostate cancer has resulted in the initiation of multiple phase II and III studies of PARP inhibitors in men with HRD prostate cancer. This extraordinary response rate justifies consideration for using this drug earlier in the disease course for HRD prostate cancers anticipated to be highly lethal.

Neoadjuvant therapy as a means to improve outcomes in prostate cancer. Early systemic therapy to address micrometastatic disease is an established paradigm. The response of primary

tumor to neoadjuvant therapy, and particularly pathologic complete response (pCR) after neoadjuvant therapy has been credentialed as a surrogate for improved outcomes in multiple malignancies, most notably bladder cancer and locally advanced breast cancer [21,22] After neoadjuvant therapy surgical resection is the only adequate means of assessing response given the limited sensitivity of imaging and biopsy to evaluate residual disease. Assessment of pCR after targeted neoadjuvant therapy is the basis for randomized studies evaluating the relative activity of targeted therapies. I-SPY and I-SPY2 have tested the addition of targeted agents to standard of care for 12 weeks prior to surgical resection as a means of assessing activity against molecularly characterized breast cancers considered to be at high risk. This approach has thus far identified two agents, including PARPi and HER inhibitors as appropriate agents for phase III study [23,24]. Although the histologies being treated are different from that proposed in this study, use of pCR as a readout for activity has demonstrated potential for identifying active and important agents for early therapy. The role of neoadjuvant therapy prior to definitive therapy for localized prostate cancer remains uncertain. Androgen deprivation therapy (ADT) concurrent and adjuvant to radiation therapy is standard of care, likely due to radiosensitizing effects of ADT (concurrent) and suppression of micrometastasis (adjuvant) in patients with high risk disease. There is no clear data that demonstrates that neoadjuvant ADT provides better outcomes compared to concurrent and adjuvant ADT with radiation. Neoadjuvant ADT prior to surgery has demonstrated that ADT alone has a low likelihood of achieving a complete response, reflecting the inability of ADT to induce apoptosis even when combined with next generation androgen receptor targeting agents [25-27]. Multiple studies from our group and others have been attempting to improve pCR by adding more effective suppressors of androgen receptor signaling, with some improvement in pCR, although at rates below the level justifying large randomized studies [28-30]. Androgen deprivation alone rarely induces prostate cancer cell apoptosis in preclinical models and patients (< 5%) in contrast to PARP inhibition which induces apoptosis in 50% of cells in preclinical models [12,31,32]. The ability to exploit synthetic lethality using PARP inhibition holds the promise of potentially more effective local and systemic control in HRD prostate cancer through induction of apoptotic cell death. As noted above, HRD tumors are more likely to metastasize early, be refractory to standard therapies and are therefore appropriate for assessment of efficacy of neoadjuvant olaparib given its activity in resistant disease. In this study, we will evaluate inhibition of a novel, and potentially critical pathway in HRD prostate cancer due to mutation and/or copy loss of the relevant gene. The impact of olaparib on the pCR rate will be evaluated and compared to the historical CR rate of 3-10% with androgen deprivation. Surgical endpoints will be evaluated, including positive margins, extracapsular extension, seminal vesicle involvement and positive lymph nodes all of which correlate with risk of progression after prostatectomy [33]. Mechanisms of resistance to PARP inhibition will be assessed in prostatectomy specimens.

1.2 Olaparib

Olaparib is a small molecule inhibitor of PARP currently approved for the treatment of HRD ovarian cancer after prior platinum therapy. Olaparib has been shown to potently inhibit PARP-1-3, and has demonstrated activity in cells, animal models and patients with BRCA 1 and 2 germline pathogenic variants [17,18]

1.2.1 Pre-clinical experience

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

1.2.2 Toxicology and safety pharmacology summary

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

1.2.3 Clinical experience

This section lists those AEs and laboratory abnormalities that are currently regarded as expected for regulatory reporting purposes.
Administration of olaparib monotherapy has been associated with reports of the following laboratory findings and/or clinical diagnoses (Table 1), generally of mild or moderate severity (CTCAE Grade 1 or 2) and generally not requiring treatment discontinuation.

Table 1 Adverse Drug Reactions from completed clinical studies

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (All CTCAE grades)	Frequency of CTCAE Grade 3 and above
Blood and lymphatic system disorders	Anaemia[a]	Very common	Very common
	Neutropenia[a]	Very common	Common
	Leukopenia[a]	Very common	Common
	Thrombocytopenia[a]	Very common	Common
	Lymphopenia[a]	Common	Uncommon
Immune system disorders	Rash[a]	Common	Rare
	Hypersensitivity[a]	Uncommon	Rare
	Dermatitis[a]	Uncommon	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia	Very common	-
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	Uncommon
	Dyspnoea[a]	Very common	Common
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhoea	Very common	Common

	Nausea	Very common	Common
	Dyspepsia	Very common	-
	Stomatitis[a]	Common	Uncommon
	Upper abdominal pain	Common	Uncommon
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Increase in blood creatinine	Common	Uncommon
	Mean corpuscular volume elevation	Uncommon	-

[a] Anaemia includes preferred terms (PTs) of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia and red blood cell count decreased; Neutropenia includes PTs of agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased; Thrombocytopenia includes PTs of platelet count decreased, platelet production decreased, plateletcrit decreased and thrombocytopenia; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Lymphopenia includes PTs of B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia and T-lymphocyte count decreased; Cough includes PTs of cough and productive cough; Rash includes PTs of exfoliative rash, generalised erythema, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic; Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity; Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis exfoliative; Dyspnoea includes PTs of dyspnoea and dyspnoea exertional; Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis. CIOMS Council for International Organization of Medical Sciences; CTCAE Common Terminology Criteria for Adverse Events; MedDRA Medical Dictionary for Regulatory Activities; SOC System organ class. MedDRA version 22.0

Summary of Risks

As of 15 June 2016, approximately 5670 patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumors are estimated to have received treatment with olaparib in AstraZeneca-sponsored, investigator-sponsored, collaborative group studies and a Managed Access Program. Olaparib has been given as either monotherapy (an estimated 3624 patients) or in combination with other chemotherapy/anti-cancer agents (an estimated 2046 patients).

Monotherapy studies

Serious adverse events

A review of the AstraZeneca Patient Safety database (which includes AstraZeneca-sponsored, investigator-sponsored/collaborative group monotherapy studies and Managed Access Program reports) as of 15 June 2016 identified a total of 1413 SAEs (1093 unblinded, 320 blinded) received from 752 patients in olaparib monotherapy studies. SAE reports of ≥1% (≥36 patients treated with olaparib/placebo monotherapy) were anemia (n=143), abdominal pain (n=40), vomiting (n=47), nausea (n=42) and dyspnoea (n=41). The most

commonly reported SAEs from these monotherapy studies were similar for the tablet and capsule formulation.

Myelodysplastic syndrome/acute myeloid leukaemia events
As of 15 June 2016, 23 reports of MDS and/or AML have been received out of a total of 5670 patients estimated to have received olaparib in the clinical study program, giving an estimated cumulative incidence of 0.41% for MDS/AML. Six additional reports of MDS/AML from 6 patients have been received from 2 blinded studies (D0816C00002 and D0818C00001) in which the treatment of the 6 patients (olaparib or placebo) is unknown. If these patients are considered to have been on olaparib treatment, the estimated incidence would be 0.51%. Of the 23 olaparib-treated patients and 6 patients on blinded treatment, the MDS/AML events have been reported in patients receiving a range of doses from both monotherapy and combination studies and for a variety of tumor types; ovarian, peritoneal or fallopian tube cancer (n= 26), breast cancer (n=1) and pancreatic cancer (n=2). Twenty-one of the 29 patients died: in 12 of these patients, MDS/AML or myelodysplasia was recorded as either a primary or secondary cause of death. In 16 patients, the event of MDS/AML is reported as not recovered (including patients that died of other causes).

As of 15 June 2016, pneumonitis has been reported in 22 olaparib-treated patients out of a total of 5670 patients estimated to have received olaparib in the clinical study program, giving an estimated cumulative incidence of 0.39%. Eleven additional reports of pneumonitis have been received from 4 blinded studies, where the treatment of the patients is unknown (7 either olaparib or placebo [D0816C00002 or D0818C00001]; 2 either olaparib + paclitaxel or placebo + paclitaxel [D081BC00004] and 2 olaparib + abiraterone or placebo + abiraterone [D081DC00008]). If these patients were considered to have been on olaparib treatment, the estimated cumulative incidence would be 0.58% (33/5670). Pneumonitis has also been reported for 1/128 (0.78%) patient randomised to placebo in Study D0180C00019, 1/62 (1.61%) patient randomised to placebo + paclitaxel in a double-blind study in recurrent or metastatic gastric cancer (Study D0810C00039) and 1/262 (0.38%) patient randomised to placebo + paclitaxel in a double-blind, phase III study in advanced gastric cancer (Study D081BC00004). The reports of pneumonitis were from patients receiving olaparib at a range of doses, given either as monotherapy or in combination with the other chemotherapy treatments. The diagnosis of pneumonitis was made whilst on treatment or within a 60-day follow-up period for all patients. The patients were treated with olaparib for ovarian cancer (n=14), breast cancer (n=4), NSCLC or small cell lung cancer (SCLC; n=7), pancreatic cancer (n=1), gastric cancer (n=4), prostate cancer (n=2) and thymic cancer (n=1).

Four of the 33 patients died due to pneumonitis (2 of these patients who were receiving olaparib in combination with liposomal doxorubicin [Study D0810L00001] and the cause of death also included pulmonary insufficiency); in 1 patient receiving olaparib and radiotherapy, the cause of death included bronchopulmonary hemorrhage, The reports of pneumonitis presented with no consistent clinical pattern and were heavily confounded by a number of pre-disposing factors (including disease under investigation, underlying pulmonary disease, pre-

existing medical conditions, smoking history and/or previous chemotherapy and radiotherapy). The majority of patients had received prior radiotherapy and/or chemotherapy and had other risk factors within the medical histories including pneumonitis, interstitial lung fibrosis, dyspnoea, hemoptysis, chest infection, allergic asthma, pleural effusion, pleural metastases, smoking. Seven patients had current SCLC or NSCLC. An independent review of available chest computed tomography (CT) scans and radiographs associated with the reports of pneumonitis concluded that there appeared to be no clear consistent clinical pattern.

MDS/AML, and pneumonitis have been identified as important potential risks for olaparib. The cumulative incidences are consistent with that expected for the patient population under study according to the available literature. These events are being closely monitored in ongoing studies. Clinical experience with olaparib is fully described in the current version of the olaparib Investigator's Brochure. Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure.

1.3 Research hypothesis

The hypothesis of this pilot study is that neoadjuvant treatment with the PARP inhibitor olaparib in men with germline or somatic HRD will induce significant tumor reduction, assessed as pCR.

1.4 Rationale for conducting this study

The frequency of HRD in prostate cancer increases substantially from the population of patients with localized prostate cancer to those with metastatic disease, reflecting the lethal phenotype mediated by HRD. Lethality is a reflection of early micrometastatic dissemination and an inability of local therapy alone to cure the disease. Men with localized prostate cancer with HRD either as a result of germline or somatic inactivation require better systemic therapy to improve their outcomes. The primary objective of this study is to assess whether the use of the PARP inhibitor olaparib prior to prostatectomy will result in pCR, which is credentialed in other malignancies as a surrogate for effective systemic elimination of tumor and long term cure. This is a pilot study to assess the feasibility of this approach in men with localized disease, with assessment of pCR, surgical margin status, extracapsular extension, seminal vesicle and nodal involvement, all of which are pathologic indicators of activity of neoadjuvant therapy. It is anticipated that the majority of patients will be known to be carriers of pathogenic germline variants, although a subset with purely somatic inactivation and HRD may identified in other ways. There is no evidence that tumors with germline vs. somatic inactivation will be differentially sensitive to PARP inhibition, so both populations will be eligible. A neoadjuvant PARP inhibitor study has not been performed in patients with prostate cancer and this study will also assess the safety and toxicity of olaparib in this patient population. If neoadjuvant therapy does not result in pCR, the remaining tissue is by definition resistant to therapy and remaining tumor tissue will be interrogated for mechanisms of resistance to inform future combination studies in advanced and localized HRD prostate cancer.

1.5 Benefit/risk and ethical assessment

The risk/benefit associated with the use of olaparib administered prior to prostatectomy must weigh the risks of the drug, both acute and long term, vs. potential benefits. The justification for adding systemic therapy for patients with HRD prostate cancer is related to the significantly increased risk of relapse and death associated with HRD. Patients who are BRCA2 carriers have a 4-5 fold increased risk of developing prostate cancer [34,35]. Once germline carriers are diagnosed with prostate cancer, their crude risk of metastasis and cancer specific mortality is increased approximately 8 fold [4-6]. Although in multivariate analysis the overall risk of cancer specific mortality decreases, the presence of a germline mutation significantly increases the risk of being diagnosed with high risk or metastatic disease reflecting an aggressive biology [6]. The frequency of other germline DNA repair genes is so low in the general population of men diagnosed with localized disease that no studies of their impact on relapse and cancer specific mortality has been carried out. Given the rarity of these variants in localized disease and the increased incidence in patients with metastatic disease, we anticipate that a similar increase in mortality attends the presence of these mutants [36]. As noted, cancer specific relapse and death after definitive therapy is essentially always related to regional nodal or systemic metastasis, which can only be addressed with better systemic treatment. The relative risk/benefit calculation for treatment men with localized HRD prostate cancer with olaparib must balance risks of morbidity and mortality of the disease with toxicities of the therapy. The risks of cancer related morbidity and mortality are outlined above. The risks of olaparib outlined in section 1.2.2 and 1.2.3 are primarily myelosuppression, which in patients with advanced prostate cancer not receiving concurrent therapy was grades 1 or 2 and nausea and vomiting grades 1 or 2[20]. In other settings the frequency of more significant toxicities, including pneumonitis, myelodysplasia and leukemia are rare (Section 1.2) and MDS/leukemia frequency is confounded by prior therapy for the majority of patients (ovarian cancer) with the DNA damaging agent platinum, and known to cause MDS/AML at a very similar frequency in this patient population [37]. There is no evidence from neoadjuvant studies of PARPi in patients with breast cancer that PARPi increases the risk of perioperative complications [24]. The use of prostatectomy in this study as definitive therapy is appropriate as there is clear evidence that radiation and prostatectomy are at least equivalent with some studies suggesting better outcomes in high risk patients [38,39]. The potential benefits of neoadjuvant PARPi for patients with HRD tumors could be reduced risk of relapse, metastasis or death which is significant in this patient population. This study will not formally evaluate long term outcomes but will provide pilot data regarding frequency of pCR, and improvement of other pathologic criteria which are predictive of relapse, as well as providing tissues which will allow interrogation of mechanisms of resistance if olaparib does not improve pCR rate.

2. STUDY OBJECTIVES

2.1 Primary objective

- To assess the pathological complete response rate following olaparib when administered as neoadjuvant therapy prior to prostatectomy in patients with localized prostate cancer containing homozygous or complementary DNA repair deficiency

The primary objective is to assess the pathological complete response (pCR) rate following olaparib when administered as neoadjuvant therapy prior to prostatectomy in patients with localized prostate cancer containing homozygous or complementary DNA repair deficiency. The rationale for this as a primary endpoint is discussed in section 1.1. Complete response after preoperative cytotoxic or targeted therapy is a surrogate for long term outcomes in bladder and breast cancer. Although not credentialed as a surrogate in prostate cancer, this appears likely due to the lack of agents which cause apoptosis in prostate cancer, and PARP inhibition has the potential for induction of apoptosis through leveraging of synthetic lethality in HRD tumors, as seen in preclinical studies.

2.2 Secondary objective

To determine the rate of positive surgical margins, extracapsular extension, positive seminal vesicles and lymph nodes at the time of prostatectomy.

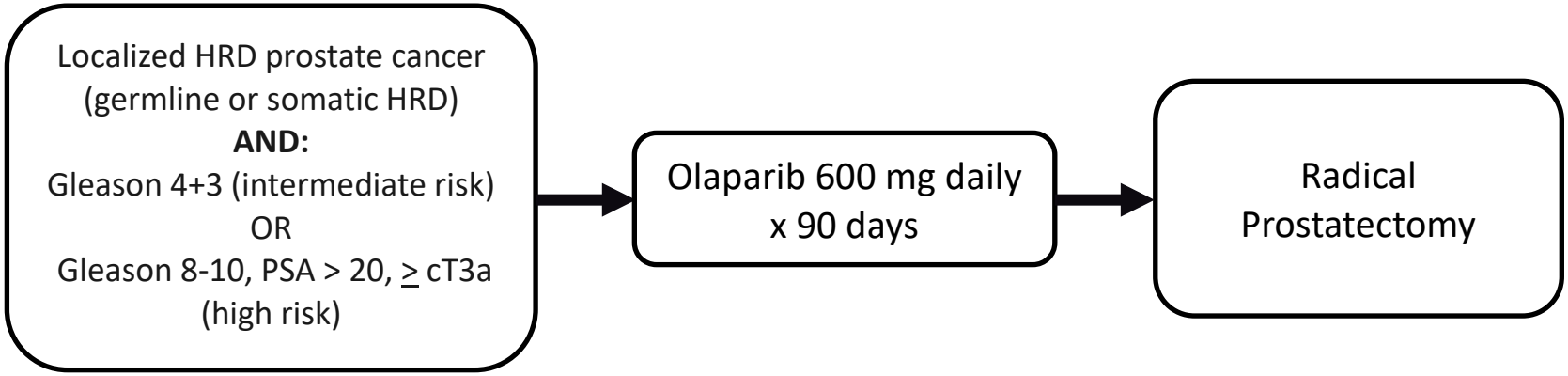
2.3 Exploratory objectives

To assess potential mechanisms of resistance to neoadjuvant olaparib by assessing residual tumor for PARP1, 53BP1, reversion mutations in BRCA1 or 2, and mutations of ERCC. These mechanisms have all been proposed as relevant mechanisms of resistance to PARP inhibition *in vitro* or *in vivo* studies.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

Figure 1 Study flow



3.2 Rationale for study design, doses and control groups

This is an open-label, single center pilot study designed to assess the pathological complete response rate following neoadjuvant therapy (olaparib) of patients with localized prostate cancer for whom radical prostatectomy is indicated. Eligible patients are those with localized prostate cancer who are referred for radical prostatectomy. Patients should be either 1) carriers of a pathogenic germline variant of a gene involved in the homologous recombination pathway of DNA repair or 2) have evidence by somatic sequencing of biallelic inactivation of a gene involved in the homologous recombination pathway of DNA repair. It is anticipated that the majority of patients will be germline carriers of a pathogenic variant of BRCA1, BRCA2 or ATM. As previously discussed these patients are at high risk of micrometastatic disease at diagnosis and are therefore appropriate for approaches designed to test therapies which might induce tumor apoptosis, using pCR as a reflection of apoptosis and potential for elimination of micrometastases.

Screening of patients for study will take place through multiple approaches. The University of Washington and Fred Hutchinson Cancer Research Center have opened a registry study offering free germline testing of all men in the state of Washington with a diagnosis of metastatic prostate cancer (GENTLEMAN study). This study will take place through website enrollment, optimizing access anywhere in the state, with germline testing kits mailed to patients for return to the center for testing. Patients with advanced disease and an identified pathogenic variant will be offered counseling, discussion of their case at precision tumor board and contact with their treating physicians regarding potential therapy with DNA damaging agents, PARP inhibitors or participation in open studies. This study is attempting to to optimize access to treatment options for these men. It is anticipated that families of these men will undergo "cascade" testing so that they will have appropriate screening for HRD related malignancy, including breast, ovarian, prostate and ovarian cancer, if they are carriers of a pathogenic germline variant. Carrier men are anticipated to undergo more intensive screening for prostate cancer and identification of localized prostate cancer in carrier men in the state of Washington[40]. The University of Washington/Seattle Cancer Care Alliance has an active breast and ovarian cancer prevention clinic for families known to be germline carriers of BRCA (Elizabeth Swisher and Larissa Korde). Male family members will be offered germline testing through a substudy of GENTLEMAN. The investigators on the current study are advisors to national advocacy groups of patients who have known BRCA and other germline mutations (FORCE – Facing Our Risk of Cancer) and currently make clinical studies available through their website, allowing nationwide recognition of the current study.

Starting on Day 1, all patients will ingest olaparib (300 mg twice daily) at the same times each day, without breaks (except as outlined for toxicity), for 90 days. The 90 day duration is chosen as a duration adequate to assess impact of neoadjuvant therapy on downstaging but not so prolonged that if patients do not respond to therapy, that potentially curative local therapy is being significantly delayed. Multiple studies have demonstrated in unselected populations that 90 day delay to surgery is not associated with any change in long term outcomes [41,42]. During neoadjuvant therapy, dose reduction of olaparib is allowed for toxicity as detailed in the protocol. Patients should receive olaparib until 1 day prior to prostatectomy, until the

patient can no longer tolerate the treatment due to an adverse event, until the patient initiates another systemic antineoplastic drug or an investigational drug, or at the discretion of the Investigator. Safety and tolerability will be documented throughout the study and 30 days after prostatectomy by assessment of adverse events, vital signs, and laboratory assessments as defined in the Schedule of Activities. All adverse events will be monitored and recorded until the Safety Follow-up visit. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI-CTCAE v4.03). In the event a patient discontinues olaparib due to a related adverse event, follow up will continue until adequate resolution of the adverse event, the physician deems the adverse event to be stable, the patient initiates another systemic antineoplastic drug or an investigational drug, or the patient withdraws consent from the study. A safety follow-up visit will be conducted approximately 30 days after the last dose of olaparib or before the initiation of a new systemic antineoplastic therapy or investigational agent, whichever occurs first. Any ongoing adverse event thought to be related to study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the Investigator as stable, the patient initiates another systemic antineoplastic drug or an investigational drug, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

Efficacy Variables

Patients will be evaluated for pathological complete response following neoadjuvant therapy, based on tissue obtained via prostatectomy.

Primary Variable(s)

The primary efficacy variable is the proportion of patients achieving a pathological complete response of localized prostate cancer. Pathologic complete response is defined as the absence of morphologically identifiable carcinoma in the prostatectomy specimen, as evaluated by the site pathologist using standard methods (see the Laboratory Manual for detailed instructions). The expected complete response rate at prostatectomy without intervention is 1% or less and is 4% to 9%, with standard androgen deprivation in a mixed population of low-to-intermediate risk disease.

Tissue may also be assessed using methodologies in addition to standard morphological analysis, however, this will not be used to downgrade a pathological complete response.

Surgical Endpoints

At the time of radical prostatectomy, pathology specimens will be assessed for surgical margins, and stage to include assessment of extracapsular extension, seminal vesicle and lymph node involvement. All of these endpoints when present represent risks for relapse after prostatectomy

Exploratory endpoints

To assess potential mechanisms of resistance to neoadjuvant olaparib by assessing residual tumor for molecular changes previously defined *in vitro* or *in vivo* to represent de novo or acquired mechanisms of resistance to PARP inhibitors. These include upregulation of the PARP1 and REV7, downregulated 53BP1 or PTIP, reversion mutations in BRCA1 or 2, and drug export by P-glycoprotein [12,43-48] These have all been proposed as relevant mechanisms of resistance to PARP inhibition in vitro and preclinical studies.

4. PATIENT SELECTION CRITERIA

4.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures

2. Men ≥ 18 years of age;

3. Histologically confirmed adenocarcinoma of the prostate without morphologic neuroendocrine differentiation or small cell features

4. The presence of homologous recombination deficiency defined by either; A) Inherited pathogenic variant of BRCA2, ATM, BRCA1, PALB2 by a CLIA level germline assay or B) have evidence by somatic sequencing using a CLIA level assay of biallelic inactivation of BRCA1, BRCA2, PALB2, FANCA or biallelic inactivation or monoallelic inactivating mutation of ATM. It is anticipated that the majority of patients will be germline carriers of a pathogenic variant of BRCA1, BRCA2 or ATM. Other germline mutations will be considered at investigator's discretion.

5. Must be candidates for radical prostatectomy and considered surgically resectable by urologic evaluation

6. No evidence of metastatic disease or nodal disease as determined by radionuclide bone scans and computed tomography (CT)/magnetic resonance imaging (MRI); non-pathological lymph nodes must be less than 20 mm in the short (transverse) axis;

7. Provided written authorization for use and release of health and research study information.

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

   - Hemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days

   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

- Platelet count ≥ 100 x 10^9/L
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN
- Patients must have creatinine clearance estimated using the Cockcroft-Gault equation of ≥51 mL/min:

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

9. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix 1).
10. Patients must have a life expectancy ≥ 16 weeks.
11. Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination throughout the period of taking study treatment and for 3 months after last dose of study drug(s) to prevent pregnancy in a partner.
12. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

4.2 Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
2. Any previous treatment with PARP inhibitor, including olaparib.
3. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years.
4. Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome
5. Patients receiving any systemic chemotherapy, hormonal therapy or radiotherapy

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

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

8. Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML.

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

10. 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, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

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

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

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

14. Patients with known active hepatitis (i.e., Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids

15. Previous allogenic bone marrow transplant or cord blood transplantation

16. Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no.3)

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3

5. STUDY CONDUCT

5.1 Restrictions during the study

5.1.1 Grapefruit juice

It is not recommended to consume grapefruit juice while on olaparib therapy.

5.1.2 Contraception

Male patients with partners of child bearing potential, who are sexually active, must agree to the use of two highly effective forms of contraception throughout period of taking study treatment and for 3 months after last dose of study drug. For details refer to Appendix C Acceptable Birth Control Methods.

5.1.3 Androgen deprivation

The use of androgen deprivation is not allowed during the neoadjuvant period

5.2 Subject enrollment and initiation of investigational product

Patients will be enrolled on study after eligibility criteria are met and begin open label olaparib within 30 days of consent. As this is a study in patients with localized prostate cancer who have not previously received treatment for malignancy, no run in period is required.

5.3 Procedures for handling subjects incorrectly enrolled or initiated on investigational product

Patients enrolled to study who are determined to have been ineligible or who develop conditions prior to administration of olaparib which are in the opinion of the principal investigator contraindications to olaparib or surgery will be removed from study.

5.4 Treatments

5.4.1 Enrollment procedure

Before or during this visit, the patient will be thoroughly informed about all aspects of the study, including all scheduled visits and activities, and will be requested to sign and date the informed consent form before any study-specific screening assessments that are not considered standard care. A patient wishing to participate must also sign the study specific HIPAA Authorization Form prior to any study-related procedures or change in treatment. The original signed and dated informed consent form must be retained by the Investigator in the patient's file and a copy must be provided to the patient. The original signed and dated HIPAA authorization form will be filed in the research chart.

Patients will be identified by their urologist, oncologist, or radiation oncologists as eligible for the study and the study will be discussed with the patient by an investigator. Patient eligibility will be assessed and confirmed by the Investigator. All inclusion criteria must be met and none of the exclusion criteria may apply. All results from the screening procedures must be available before determining a patient's eligibility for the study.

Protocol-specified procedures at the Screening visit must occur within 28 days of enrollment, unless otherwise noted in the Schedule of Activities; otherwise the Screening visit must be repeated. Assessments performed as standard-of-care within the screening window may be used for screening.

The following procedures will be performed during the Screening period unless otherwise noted:

- Informed consent (before or during the Screening visit and within 28 days of enrollment);
- Assign screening number;
- Medical history and demographics including PSA history, currently active conditions, and significant inactive conditions;
- Record concomitant medications including all vitamins, herbal remedies, over the counter medications, nutritional supplements, and prescription medications used by the patient for up to 7 days preceding the Screening evaluation;
- Laboratory assessments (hematology and chemistry)
- PSA
- Complete physical examination
- Digital rectal examination (if not already performed by urologist)
- ECOG performance status
- 12-lead ECG
- PT/PTT
- Testosterone
- Vital signs (heart rate and systolic and diastolic blood pressures)
- Weight will be recorded at every visit. Height will be recorded at the Screening visit only;
- Assess tumor and document clinical stage of disease. Patients will undergo bone scan and CT/MRI of the pelvis if defined as having high risk disease or at the investigator's discretion.
- Review inclusion and exclusion criteria and determine if the patient is eligible for the study;

5.4.2 Study Evaluations

Baseline (Day 1)

- Limited physical examination

- Vital signs including temperature, blood pressure, and heart rate; weight if performed ≥ 96 hours prior;
- Laboratory assessments (hematology and chemistry) if screening assessments were done >28 days prior;
- Blood will be collected for circulating tumor DNA/serum
- Update concomitant medications listing;
- Instruct patient to self-administer olaparib at approximately the same times every day. Instruct patient to return all unused tablets at the end of each treatment period to assess compliance;
- Adverse event review.

5.4.3 Day 30 (± 5 Days), 60 (± 5 Days) 90 (± 5 Days) Visits

- Vital signs including weight, temperature, blood pressure, and heart rate;
- ECOG performance status;
- Safety laboratory assessments (chemistry and hematology);
- PSA
- Plasma and Serum will be collected and frozen
- Update concomitant medications listing;
- Adverse event review;
- Assess drug compliance for olaparib;
- Dispense olaparib (30-day supply as indicated)
- Day 30, 60, 90 limited physical examination (directed towards patient reported symptoms; and cardiac, respiratory, and gastrointestinal systems)

5.4.4 Radical prostatectomy

Day 90 (± 14 Days)

- Tissue will be obtained per standard procedures

5.4.5 End of study visit (Day 120 (± 5 Days)

- Vital signs including weight, temperature, blood pressure, and heart rate;
- Safety laboratory assessments (chemistry and hematology);
- PSA
- Plasma and Serum will be collected and frozen
- Adverse event review
- Pathologic stage review/documentation

5.4.6 Early Termination Visit (Early Cessation of Study Drug)

Patients will be advised in the written informed consent that they have the right to withdraw from the study at any time without prejudice. The Principal Investigator or the Sponsor may discontinue a patient from study in the event of an intercurrent illness, adverse event, other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation, non-compliance, protocol violation, or other administrative reasons.

For patients who have started study drug and terminate the study prematurely, every effort should be made to ensure the collection of safety data by means of unscheduled visits, the frequency and timing of which will be determined by the Principal Investigator, and the follow-up visit. If the patient is withdrawn from the study because of an adverse event or a serious adverse event, the event(s) must be followed as per section 6.4.3.

Patients who discontinue the trial prematurely may be replaced at the discretion of the Investigator.

5.4.7 Identity of investigational product

The AstraZeneca Pharmaceuticals will supply olaparib to the investigator

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

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

5.4.8 Dose and treatment regimen

Olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib will be dispensed to patients on Day 1 and approximately every 28 days thereafter until the patient completes the study, withdraws from the study or closure of the study.

Study treatment is available in the form of film-coated tablets containing 100 or 150 mg of olaparib.

Patients will take olaparib orally twice daily at 300 mg bid continually. 300 mg olaparib tablets should be taken 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.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Dose Reductions

For guidance on dose reductions for management of AEs refer to section 5.4.11

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see section5.5

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 of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200mg BD.

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.

5.4.9 Storage

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

5.4.10 Management of toxicity of olaparib

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion, until improved Hb ≥10 g/dl. If the interruption is any longer, the study team must be informed. Upon recovery, study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step in the case of repeat Hb decrease. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

Once dose is reduced, escalation is not permitted.

5.4.11 Management of hematological toxicity

5.4.11.1 Management of anemia

Table 2 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 4 weeks. If repeat Hb**< 10 *but* ≥ 8 g/dl**, dose interrupt (for max of 4 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 4 weeks. until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 6.7.1.3 for the management of this.

5.4.11.2 Management of neutropenia, leukopenia and thrombocytopenia

Table 3 Management of neutropenia, leukopenia and thrombocytopenia

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

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

Primary prophylaxis with Granulocyte colony stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be

stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

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

For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section 6.7.1.3.

5.4.11.3 Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence

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

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

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

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

5.4.12 Management of non-hematological toxicity

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

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

5.4.12.1 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 Study Physician.

5.4.12.2 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie 2 pieces of toast).

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

5.4.12.3 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 AZ study physician.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped 1 day before prostatectomy. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

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

Table 4 Dose reductions for study treatment

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

5.5 Concomitant and post-study treatment(s)

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

Medications that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

Live virus and live bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

Restricted concomitant medications

Strong or Moderate CYP3A inhibitors

Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib.

If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use.

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100mg bid 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 150mg bid 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 CYP3A inducers (eg. bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib.

If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib.

If a patient requires use of a strong or moderate CYP3A inducer or inhibitor then they must be monitored carefully for any change in efficacy of olaparib.

P-gp inhibitors

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

Effect of olaparib on other drugs

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

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

The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.

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

Examples of substrates include:

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

Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

Anti-emetics/Anti-diarrheals

If a patient develops nausea, vomiting and / or diarrhea, then these symptoms should be reported as AEs 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.

5.5.1 Medications that may NOT be administered

No chemotherapy, immunotherapy, hormonal therapy or other novel agent is to be permitted while the patient is receiving study medication.

5.6 Treatment compliance

5.6.1 Accountability

At each study visit patients will be asked about missed or lost doses. Pill diaries will be completed by the patients while on study. Pill bottles and any unused medications will be returned by the patient at each study visit. If diary is not returned at the time of the visit, the patient will be required to send the pill diary to the research coordinator. The investigational drug service (IDS) will count returned pills; the pill diaries and pill counts will be reconciled by the study coordinator using drug accountability CRF. Treatment compliance will be defined as the number of tablets taken during the study divided by the expected number of tablets, multiplied by 100%. Tablets that are not returned will be considered to have been taken, unless otherwise reported by the patient as not having been taken. Unused pills will be destroyed on site by the IDS.

5.7 Discontinuation of investigational product

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

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

Adverse Event

Severe non-compliance with the study protocol

Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)

5.7.1 Procedures for discontinuation of a subject from investigational product

If patient is discontinued from olaparib for one month continuous duration due to toxicity or other conditions, the patient will proceed to prostatectomy as clinically indicated.

5.8 Withdrawal from study

Patients may withdraw from study at any time. Patients who are unable to receive more than 6 weeks of olaparib prior to prostatectomy will be replaced to reach total target enrollment.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

Data delineated in section 5.4 will be collected and will also be entered into a study specific Redcap database for collation of patient characteristics and adverse events. Patients will maintain pill diaries which will be returned at each study visit and reconciled by the research coordinator and IDS as previously described. Pathologic stage at prostatectomy will be as per the pathology report by site pathologist and kept in the study binders.

6.2 Efficacy

The primary endpoint is to determine the pathologic complete response induced by the administration of olaparib at approximately 90 days (12 weeks). The primary efficacy analysis will estimate the proportion of patients who achieve a pathological complete response after neoadjuvant therapy upon radical prostatectomy. Pathologic stage (and complete response) will be assessed by pathologists at the institution. The detailed procedures for assessment of pathologic endpoints is contained in the laboratory manual.

6.3 Safety

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

6.3.1 Definition of adverse events

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). 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.

6.3.2 Olaparib adverse events of special interest

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

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

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

6.3.3 Definitions of serious adverse event

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

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

6.3.4 Recording of adverse events

Adverse events will be assessed at study visits and if necessary, at unscheduled evaluations.

Time period for collection of adverse events

Adverse events and SAE will be collected from the time of patient consent until 30 days after prostatectomy.

6.3.4.1 Adverse events after the 30 day follow up period

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

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

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and/or post study completion then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise, after study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days).

Follow-up of unresolved adverse events

Adverse events will be followed until resolution or until the investigator determines that the adverse event is not expected to return to baseline.

The following variables will be collected for each AE:

AE (verbatim)
The date when the AE started and stopped
NCI CTCAE grade and the maximum CTC grade attained
Whether the AE is serious or not
Investigator causality rating against the Investigational Product (yes or no)
Action taken with regard to investigational product/comparator/combination agent
Outcome.

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

Date AE met criteria for serious AE
Date Investigator became aware of serious AE
AE is serious due to
Date of hospitalization
Date of discharge
Probable cause of death
Date of death
Autopsy performed

Description of AE
Causality assessment in relation to Study procedure(s)
Causality assessment in relation to Other medication

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.3. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Note: Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix B 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Disease progression

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

New cancers

The development of a new primary cancer (including skin cancer) should be regarded as an AE (see Olaparib Adverse Events of Special Interest). New primary malignancies are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

Lack of efficacy

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

Deaths

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

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

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.3.5 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.

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

6.3.5 Reporting of serious adverse events

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

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

External Scientific Research (ESR)
The investigator IND number assigned by the FDA
The investigator's name and address
The trial name/title and AstraZeneca ESR reference number

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

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

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

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

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

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

6.3.6 Laboratory safety assessment

Full hematology assessments for safety (hemoglobin, red blood cells (RBC), platelets, mean cell volume (MCV), median cell hemoglobin concentration (MCHC), mean cell hemoglobin (MCH), white blood cells (WBC), absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials. Coagulation, activated partial thromboblastin time (APTT) and international normalized ratio (INR) will be performed at baseline and if clinically indicated unless the patient is receiving

warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time, INR and APTT, be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Biochemistry assessments for safety (sodium, potassium, calcium, magnesium, random glucose, creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], and total protein will be monitored per the schedule of activities.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities as defined in Section 5.4.11. These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

Abnormal laboratory values which fall with the ranges defined as requiring dose modification (Section 6.4.11) will be addressed as described.

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

For blood volume see Section 7.1.

6.3.7 Physical examination

A complete physical examination includes assessment of the following; General appearance, respiratory, cardiovascular, abdomen, skin, head and neck, lymph nodes, spine and extremity and neurologic systems. Complete physical examination will occur at screening, baseline, 90 day visit prior to prostatectomy and at the time of any evaluations outside of scheduled visits for toxicity or progression. Limited physical examination is directed towards patient reported symptoms; and cardiac, respiratory, and gastrointestinal systems. This will occur at 30 and 60 day visits.

6.3.8 ECG

6.3.8.1 Resting 12-lead ECG

ECGs are required within 28 days prior to starting study treatment and when clinically indicated.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected. Heart rate, P and QRS durations, PR, QT and QTc intervals will be recorded from standard lead of the computerized quantitative 12-lead ECG.

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

6.3.9 Vital signs

Vital signs will be performed as per the schedule of events (Table 6)

6.3.9.1 Pulse and blood pressure

Blood pressure and pulse rate will be measured using standard clinic vital signs monitoring devices or with cuff in the clinic rooms. For timings of assessments refer Schedule of events (Table 6)

6.3.9.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Plan and Time Schedule (Table 6)

6.3.10 Other safety assessments

6.3.10.1 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 as defined in Section 5.4.11. 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.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 5 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	**Clinical chemistry**	5	5	25

Table 5 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
	Hematology	3	5	15
	Coagulation	2	1	2
	PSA	3	4	15
Biomarker	**ctDNA/serum**	20	5	100
Total		33	21	157

7.2 Handling, storage and destruction of biological samples

7.2.1 Circulating DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached (15 years).

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data. No personal details identifying the individual will be available to any person (AstraZeneca employee or laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrollment code and the DNA number will be maintained and stored in a secure environment, with restricted access. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the subject has requested disposal/destruction of collected samples not yet analyzed.

7.3 Chain of custody of biological samples

The Principal Investigator ensures that samples are labelled and stored in accordance with the Laboratory Manual. The PI keeps traceability of the samples while in storage until disposed of or used in entirety.

7.4 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent for the use of their donated samples, their unused samples will be disposed of/destroyed, and the action documented. In the event some or all of their samples have already been used at the time of consent withdrawal, data from these samples may still be included in the study analysis at the Investigator's discretion.

The Principal Investigator:

Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site

Ensures that the subject is informed about the sample disposal.

The Principal Investigator must notify AstraZeneca if consent is withdrawn.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

8.3 Ethics and regulatory review

The Cancer Consortium IRB provides ethics oversight and should approve the final clinical study protocol, including the final version of the informed consent form and any other written information and/or materials to be provided to the patients. This will include an approval of the exploratory biomarker research. The investigator will ensure the distribution of these documents to the applicable review committees and study staff.

8.4 Informed consent

The principal investigator will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and the biomarker research components.

- Ensure that each patient is notified that they are free to withdraw from the study or the research components at any time

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure that each patient provides signed and dated informed consent before conducting any procedure specifically for the study

- Ensure each original, signed informed consent form is stored in the Investigator's study file

- Ensure a copy of each signed informed consent form is given to the patients

Subjects may withdraw at any time from study.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without mutual agreement of the Principal Investigator and AstraZeneca. If there are any substantial changes to the protocol, then these changes will be documented in a protocol amendment and where required in a new version of the protocol. The amendment should be approved by the IRB and any other applicable authorities before implementation. Local requirements should be followed for revised protocols.

If a protocol amendment requires a change to the informed consent form, AstraZeneca and the center's IRB should approve the revised consent form before it is used.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, regulatory authories or IRB committee may perform audits or inspections, including source data verification. The purpose of an audit is to systematically and independently examine all study activities and documents to determine whether these activities were conducted and data were receord, analyzed and reported according to Good Clinical Practice (GCP) guidelines of the International Conference on Harmonisation (ICH) and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection.

9. STUDY MANAGEMENT

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will visit the study site to review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also to train them in any study specific procedures. The Principal Investigator will ensure that appropriate training relevant to the study is given to all of the staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all staff members involved in the study.

9.2 Monitoring of the study

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

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

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

9.3 Source data

Source data will be maintained as a combination of the electronic medical record and/or paper CRFs in the patient's study binder which will kept in a secure location at UW/SCCA and in a password protected REDCAP database.

9.4 Study timetable and end of study

Enrollment is projected to be 36 months from the time of IRB approval and End of Study/Last patient visit to be four months later.

9.5 Data management

Data management will be performed using paper CRFs and subsequently recorded in institutional REDCAP database.

Adverse events and medical/surgical history will be classified according to the terminology of CTCAE 4.03 and the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the MedImmune/ AstraZeneca Drug Dictionary. Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

10. EVALUATION AND CALCULATION OF VARIABLES

10.1 Calculation or derivation of efficacy variable(s)

At the time of prostatectomy the pathologic stage will be assessed by the site pathologists, including presence or absence of detectable tumor on histology. Pathologic complete response will be based purely on light microscopy without immunohistochemistry. The pathologic stage T0-T4, presence or absence of margin involvement (R0 vs .R1), presence or absence of nodal metastasis (N0 vs. N1) Calculation or derivation of safety variable(s).

Tumor load is a metric that may be explored if there is evidence of downstaging and will be calculated using 1) largest cross-sectional dimension of tumor in reconstructed "whole cross-sectional slices," with minimal residual disease (MRD) defined as ≤ 0.5 cm; and 2) RCB, with tumor volume calculated by using 3D volume estimation based on the largest cross-sectional tumor dimension and number of cross-sections involved by tumor, corrected for tumor cellularity, with MRD defined as RCB ≤ 0.25 cc (TV ≤ 0.5 cc × TC ≤ 50%). Residual tumor volume will be determined and analyzed as both a continuous and dichotomized variable as a function of type of therapy, residual androgen receptor signaling and subsequent analyses of PSA relapse that may be performed in the future. Pathologic complete response, defined as the absence of morphologically identifiable carcinoma in the prostatectomy specimen, will be determined following radical prostatectomy. A needle biopsy will be reviewed initially to confirm malignancy. The evaluation of prostatectomy specimens without residual cancer will be based on ISUP working guidelines for specimen handling (Samaratunga et al, 2011) and modified as appropriate for postneoadjuvant treatment. Atypical foci should be immunostained for alpha methyl CoA racemase (AMACR) and basal cell markers, and cytokeratin and prostate specific antigen (PSA), where appropriate. If no cancer is found in the radical prostatectomy specimen after detailed examination, the tumor should be classified as pT0 (pathologic complete response).

Gleason scoring of the prostatectomy sample will be performed, however may not be appropriate as is the case following treatment with hormonal therapy. However, morphologic tumor response will be documented by applying post therapy histologic classification according to the guidelines of the MD Anderson Cancer Center (Efstathiou et al, 2010).

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, ECG changes. These will be collected for all subjects. Summaries of data will be presented.

10.2 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgment, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such. A similar review of laboratory/vital signs/ECG data may be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

There are currently no identified OAEs for olaparib.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

11.1.1 Efficacy Analysis Set

Patients who receive olaparib for the complete planned neoadjuvant cycle and proceed to prostatectomy with tissue available for analysis of pathologic endpoints will be the efficacy analysis set. Patients who do not complete the treatment regimen or do not proceed to prostatectomy may be replaced in order to reach the target accrual for efficacy after discussion with principal investigator and sponsor

11.1.2 Safety Analysis Set

Patients who have receive at least one dose of treatment and are evaluable for toxicity will be included in the Safety Analysis Set

11.2 Determination of sample size

This is a pilot study assessing whether PARP inhibition with olaparib has the capacity to induce high pathologic complete respone (pCR) rates in men with tumors harboring DNA repair deficiencies (i.e. induce synthetic lethality). The primary efficacy endpoint will be the pCR rate as determined on prostatectomy specimens following 12-weeks of neoadjuvant olaparib. The historical complete response rate to 3-8 months of androgen deprivation with LHRH agonist and androgen receptor antagonist is ~10% (H0). We anticipate a complete response rate of ≥40% (H1) following 12-weeks of olaparib in patients with homologous DNA repair deficient tumors (truncal mutations/copy loss). Therefore, a sample size of 15 patients would yield 80% power to detect a difference between the null and alternative pathologic complete response rates at a two-sided alpha = 0.05

11.3 Methods of statistical analysis

Statistical analyses will be performed using all patients with evaluable data (e.g., pathologic staging among those who had a prostatectomy, and safety data among those who receive a dose of olaparib).

For efficacy analysis pathologic complete response is defined as the absence of morphologically identifiable carcinoma in the prostatectomy specimen, as evaluated by the site pathologist using standard methods. Formalin-fixed, paraffin-embedded slides will be evaluated by a central pathology review at completion of the study. Comparison of the actual pathologic complete response rate with the historial rate of 10%.

For safety analyses, all patients who received at least one dose of study drug and had at least one post-baseline safety assessment will be evaluated. Data will be descriptive, describing frequency of grade 1-5 adverse events. Data from all cycles of treatment will be combined in the presentation of safety data. AE will be listed individually by subject. The number of subjects experiencing each AE will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of subjects with adverse events in different categories (e.g. causally related, CTCAE grade ≥3 etc.) will be summarized. Any AE occurring before the first dose of investigational product (i.e. before study Day 1) will be included in the data listings but will not be included in the summary tables of adverse events. Any AE occurring within the defined 90 day follow-up period after discontinuation of olaparib will be included in the AE summaries. Hematology, clinical chemistry, vital signs, ECG data, demographic data, medical histories and concomitant medications will be listed individually by subject. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used. Details of any deaths will be listed for all subjects.

12. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

12.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a SAE and is to be reported as such. In the case of a medical emergency the investigator may contact the Study Team Physician.

12.2 Overdose

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

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

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

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

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

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

12.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

12.3.1 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

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

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Table 6 Schedule of Assessments

Study Day	-28 to -1	Baseline 1	30 (±5 days)	60 (±5 days)	90 (±5 days)	Surgery 90 (±14 days)	Unscheduled visits[a]	End of study[b]
Obtain written informed consent	X							
Medical history, demographics, PSA history	X							
Physical examination [c]	X	[X]	X	X	X		[X]	X
Digital rectal examination [d]	X						[X]	
ECOG Performance Status	X	[X]	X	X	X		[X]	X
Disease staging (CT/MRI, bone scan)[e]	X						[X]	
Inclusion/exclusion review	X	X						
Obtain weight, height, vital signs [f]	X	[X]	X	X	X		[X]	X
Obtain ECG[l]	X				X		[X]	
Hematology and chemistry [g]	X	[X]	X	X	X		[X]	X
PSA	X	[X]	X	X	X		[X]	
PT/PTT	X	[X}						
Research blood [h]		X	X	X	X		[X]	X
Adverse event review		X	X	X	X		X	X
Concomitant medication	X	X	X	X	X		X	X
Dispense oral study drug(s)[i]		X	X	X	[X]			
Study drug(s) accountability			X	X	X		[X]	
Archival Tissue Sample [j]	X							
Prostatectomy [k]						X		

NOTE: [X] denotes an optional procedure for that day.

[a] Unscheduled visits can be performed at any time to assess the patient for an adverse event or at the discretion of the Investigator.

[b] The safety follow-up visit will be conducted approximately 30 days (± 5 days) after the last dose of Olaparib or prior to the initiation of a new systemic antineoplastic therapy or investigational agent, whichever occurs first.

[c] Patients will undergo a complete physical examination at the Screening visit and Day 90 visit. For other assessments: limited physical examination (directed towards patient reported symptoms; areas of cancer spread; and cardiac, respiratory, and gastrointestinal systems).

[d] Digital rectal examination should be performed either by the urologic surgeon or the investigator, if not previously performed.

[e] Patients will undergo bone scan and computerized tomography (CT)/magnetic resonance imaging (MRI) of the pelvis if defined as having high risk disease or at the investigator's discretion. Any evaluable and measurable disease must be documented within 4 weeks prior to enrollment with a CT scan and/or bone scan (bone scans obtained within 8 weeks will be acceptable). Imaging of the chest, abdomen or head should be performed if clinically indicated.

[f] Height only at baseline. Weight and vital signs (blood pressure, heart rate, and temperature) will be taken at each visit. These assessments do not need to be repeated at the Baseline Visit if screening assessments were completed ≤4 days prior to first dose.

[g] Blood will be collected and sent to the local laboratory for the analysis of the following: clinical chemistry, hematology, PSA, serum testosterone. Baseline: collect if screening assessments were done > 28 days prior. Additional blood will be collected at Baseline and followup visits for ctDNA and plasma.

[h] Research blood drawn per laboratory manual

[i] Therapy will continue for 90 days and be discontinued 1 day before prostatectomy for all patients. If prostatectomy is delayed, dispense an additional bottle of olaparib.

[j] Tissue from the diagnostic biopsy will be requested (tissue blocks wherever possible; if not possible, 10 unstained slides are to be sent to the study site. See the Lab Manual for processing instructions. Pathology report (including the assessment of the local pathologist regarding Gleason score) from diagnostic biopsy must accompany registration materials.

[k] Radical prostatectomy should occur on Day 90; a window of ±14 days is permitted, however oral dosing should continue until 1 day before surgery. Preoperative and postoperative evaluation and treatment will be administered as per the instructions of the surgeon.

[l] ECG is required within 28 days prior to starting study treatment and when clinically indicated.

Appendix A: Eastern Cooperative Oncology Group Performance Status

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

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

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 5.4.13 of the protocol.

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

The Investigator participates, 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, olaparib).

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

Definitions

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

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

Identification of Potential Hy's Law Cases

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

- ALT ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

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

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

Follow-up

Potential Hy's Law Criteria not met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

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

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

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

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

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

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

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

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

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 C Acceptable Birth Control Methods

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

- Women of childbearing potential and their partners, 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).

- Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination (as listed below), throughout the period of taking study treatment and for 3 months after last dose of study drug(s) due to the unknown effects of the study drug on the sperm, or they must totally/truly abstain from any form of sexual intercourse (see below). Male patients should not donate sperm throughout the period of taking study treatment and for 3 months following the last dose of study drug(s).

Acceptable Non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must continue for the total duration of study treatment and for at least 1 month after the last dose (for 3 months after last dose for male patients). Periodic abstinence (eg, calendar ovulation, symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomized sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD PLUS male condom. Provided coils are copper-banded

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (e.g., 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 (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom