# BrUOG 337: Olaparib Prior to Radical Prostatectomy For Patients with Locally Advanced Prostate Cancer and Defects in DNA Repair Genes

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## 1.0 OBJECTIVE

### 1.1 Primary Objective

1.1.1. To evaluate the Prostate Specific Antigen (PSA) response rate of olaparib prior to radical prostatectomy for patients with locally advanced prostate cancer and defects in DNA repair genes.

### 1.2 Secondary Objectives

1.2.1 To evaluate the PSA progression-free survival of olaparib and radical prostatectomy for patients with locally advanced prostate cancer and defects in DNA repair genes.

1.2.2 To evaluate the safety of olaparib prior to radical prostatectomy for patients with locally advanced prostate cancer

1.2.3 To evaluate the rate of defects in DNA repair genes in patients with newly diagnosed locally advanced prostate cancer.

## 2.0 BACKGROUND

**BACKGROUND**

**High Risk Prostate Cancer:** Patients with prostate cancer and high risk features are at substantial risk for relapse following radical prostatectomy.[1-3] In a study of 369 patients with positive lymph nodes identified after radical prostatectomy and extended lymph node dissection the 10 year freedom from recurrence was only 28%. Patients with seemingly localized prostate confined disease, such as those with T2c disease but with high risk features such as a PSA >20 or Gleason grade 8-10, have a 40% recurrence rate.[4] Emerging data suggest that aggressive use of radical prostatectomy for patients with extra-prostatic extension, and extended pelvic lymph node dissection in patients with lymph node involvement, may be beneficial.[6-11] However, effective systemic adjuvant therapies are desperately needed to improve outcomes in combination with these aggressive surgical approaches.

**Adjuvant Androgen Deprivation Therapy (ADT) and Chemotherapy After Radical Prostatectomy:** The role of adjuvant hormone therapy in patients who undergo radical prostatectomy is modest. An improvement in biochemical failure-free survival without an improvement in overall survival was noted in RTOG 85-31,[12] while a modest survival benefit was noted by Messing et al.[13]

It was hoped that combination next generation hormone therapy would be beneficial in the perioperative setting but this promise has not been fulfilled. Efstathiou et al performed a neoadjuvant study of 24 weeks of abiraterone+ enzalutamide +LHRH antagonist versus abiraterone +LHRH antagonist (randomized 2:1) in pts with LHRPC (clinical stage T1c/T2 with biopsy Gleason ≥ 8, or ≥ T2b with Gleason ≥ 7 and PSA > 10 ng/mL).[14] The primary outcome was the effect on pathologic stage. Pathologic downstaging ( ≤ pT2N0) occurred in 13/44 (30%) abiraterone + enzalutamide+ LHRH antagonist patients (no pathologic complete responses) versus 11/21 (52 %) abiraterone +LHRH antagonist (p = 0.07) including 2 pathologic complete responses.[14] These findings do not favor adding enzalutamide to augment abiraterone +LHRH antagonist efficacy in localized high risk prostate cancer and there was a trend for inferior outcome.

Similarly adjuvant docetaxel was not helpful. In the phase III trial SPCG2 459 patients were randomized to receive either 6 cycles of adjuvant docetaxel (Arm A) or surveillance (Arm B). Primary end-point was a rising PSA >0.5ng/ml. High-risk prostate cancer was defined as pT2 with a positive margin if Gleason

score (GS) 4+3 or higher, pT3b >GS 3+4 or any lymph node positive disease with >GS 3+4. Patients were followed for 5 years with PSA every 3 months. The biochemical relapse rate was 47.9% in the docetaxel group and 38.9% in the observation group.[15]

**PARP Inhibition: Targeting DNA repair defects in Prostate Cancer:**

DNA damage occurs continuously in all living cells as a result of oxidative damage or DNA replicative stress.[16] Poly ADP ribose polymerase 1(PARP1) PARP1 plays a critical role in restoration of genomic integrity by facilitating efficient repair of DNA breaks.[17] Inherited defects in DNA repair pathways result in increased susceptibility to the development of malignancy.[18] For example inactivating mutations in BRCA1 and BRCA2, which are required for efficient DNA double stranded repair, significantly increase the risk of breast, ovarian and prostate cancer.[19] Approximately 23% of metastatic prostate cancer have aberrations of BRCA 1 and BRACA 2.[20] PARP inhibitors specifically target oncogenic cells with DNA repair deficiency and ultimately lead to their cell death from over accumulation of double stranded DNA breaks in the nuclei.[16-19] PARP inhibitors can prevent the disassembly of PARP protein from DNA complexes; this has been shown to be highly toxic to a cancer cell with a DNA repair abnormality. [19]

There is substantial data indicate that PARP inhibitors possess antitumor activity within patient populations with DNA repair deficiency. For example phase I/II studies have demonstrated activity of olaparib in patients with breast, ovarian and prostate cancer with BRCA1 and BRCA2.[21,22] Olaparib has been FDA approved for women with a BRCA mutation and metastatic ovarian cancer.

**Olaparib:**

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB). Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

PARP inhibition is a novel approach to targeting tumours 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). Tumours with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and BRCA2 defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo, [23,24] and in the clinic.[25] The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair. [26,27] 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 tumour 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.

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

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

*Clinical experience - Emerging Safety Profile and Reference Safety Information. (This section lists those ADRs that are currently regarded as expected for regulatory reporting purposes.)*
A description of the emerging safety profile for olaparib, with guidance for investigators, is provided in Section 6 of the IB. Olaparib monotherapy has been associated with laboratory findings and/or clinical diagnoses, generally of mild or moderate severity (CTCAE Grade 1 or 2) and generally not requiring treatment discontinuation. The safety profile is based on pooled data from 1248 patients treated with olaparib monotherapy in clinical trials in the therapeutic indication at the recommended dose. The following adverse reactions have been identified in completed clinical trials with patients receiving olaparib monotherapy where patient exposure is known.

Adverse Drug Reactions are organized by Medical Dictionary for Regulatory Activities (MedDRA) SOC and then by MedDRA preferred term in Table 41. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); and very rare (<1/10,000) including isolated reports.

| 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] | Common | Common |
| | Thrombocytopenia[a] | Common | Common |
| | Leukopenia[a] | Common | Common |
| | Lymphopenia[a] | Uncommon | Uncommon |
| Immune system disorders | Rash[a] | Common | - |
| | Hypersensitivity[a] | Uncommon | - |
| | 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 | - |
| Gastrointestinal disorders | Vomiting | Very common | Common |
| | Diarrhoea | Very common | Common |
| | Nausea | Very common | Common |
| | Dyspepsia | Very common | - |
| | Stomatitis | Common | Uncommon |
| | Upper abdominal pain | Common | Uncommon |
| General disorders | Fatigue (including asthenia) | Very common | Common |
| Investigations | Increase in creatinine | Common | Uncommon |
| | Mean corpuscular volume elevation | Uncommon | - |

Description of selected adverse reactions Hematological toxicity Anemia and other hematological toxicities are generally low grade (CTCAE Grade 1 or 2), however, there are reports of CTCAE Grade 3 and higher events. Anemia was the most common CTCAE Grade ≥3 adverse reaction reported in clinical studies with first onset generally reported in the first 3 months of treatment. An exposure-response relationship between olaparib and decreases in hemolobin has been demonstrated. In clinical studies with olaparib, the incidence of CTCAE Grade ≥2 shifts (decreases) from baseline in hemoglobin was 20%, absolute neutrophils 15%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate). The incidence of elevations in MCV from low to normal at baseline to above the upper limit of normal was approximately 55%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences. Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment with olaparib, and periodically after this time to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment.

Other laboratory findings in clinical studies with olaparib the incidence of CTCAE Grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 15%. Data from a double-blind placebo-controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae; 90% of patients had creatinine values of CTCAE Grade 0 at baseline and 10% were CTCAE Grade 1 at baseline. Nausea and vomiting Nausea was generally reported very early, with first onset within the first month of olaparib treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of olaparib treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients. Combination studies Safety data from studies in which olaparib has been administered in combination with other agents are discussed in Section 5.2.4 of the IB. The degree of bone marrow suppression observed in some patients in the combination studies has however been greater than would be expected with the chemotherapy agent alone, as per label information. Myelotoxicity has been observed in studies evaluating olaparib with the following combination therapies: DTIC; carboplatin; paclitaxel; carboplatin + paclitaxel; gemcitabine; topotecan; cisplatin; doxorubicin, cisplatin + gemcitabine; or irinotecan.

Adverse events of special interest

*Myelodysplastic syndrome/acute myeloid leukemia:* The incidence of MDS/AML in patients treated in clinical trials with olaparib monotherapy, including long-term survival follow-up, was <1.5% and the majority of events had a fatal outcome. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging treatments. The majority of reports were in germline BRCA mutation carriers and some of the patients had a history of previous cancer or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with olaparib, it is recommended that olaparib should be discontinued and the patient be treated appropriately.

*New Primary Malignancies other than MDS/AML:* New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented BRCA mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents.

*Pneumonitis:* Pneumonitis has been reported in <1.0% patients treated with olaparib monotherapy in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). When olaparib was used in clinical studies in combination with other therapies there have been events with a fatal outcome. If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or anabnormal chest radiologic finding is observed, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately.

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

**Olaparib in Patients with Prostate Cancer and Defects in DNA Repair Genes:**

The Trial of PARP Inhibition in Prostate Cancer (TOPARP-A) evaluated olaparib in patients with prostate cancer and DNA repair deficiency.[28] The primary endpoint was response rate (either objective radiographic response, 50% reduction in PSA level, or reduction in circulating tumor cells. All patients were hormone refractory and had received docetaxel and most had been treated with abiraterone or

enzalutamide (98%). Fifty patients were entered. Overall 16 of 49 (33%) evaluable patients were biomarker positive indicative of alterations in one of the following DNA repair genes -BRCA1/2, ATM, Fanconi anemia genes, or CHEK2. Of the 16 patients with deleterious changes in DNA repair genes, 14 (88%) responded to olaparib. The median survival was 13.8 months for biomarker positive patients as compared to 7.5 months for biomarker negative patients.[28] Toxicity including grade 3 or 4 anemia (10/50), fatigue 6/50), thrombocytopenia (2/50) and neutropenia (2/50).

**PSA For Determining Response/Progression in Prostate Cancer:**
**A 25% increase in Serum PSA from baseline and a 50% fall in serum PSA has become a standard criteria for assessing progression/response in prostate cancer, [29] since radiographic measurement by RECIST criteria are very difficult in prostate cancer. The criteria were used in the phase III TAX327 prostate cancer trial and other phase III trials. [30,31] The TOPARP-A trial with olaparib also utilized PSA as the primary determinant of response. [28]**

**Summary of Proposal:**
This protocol will evaluate the use of olaparib prior to radical prostatectomy for patients with locally advanced prostate cancer and defects in DNA repair genes. Tumor tissue and peripheral blood (peripheral blood is not required, just highly recommended) will be sent to Foundation Medicine, Cambridge Massachusetts, for genomic analysis. Patients found to have DNA defects (as assessed in tumor tissue via the FoundationOne assay or cell-free DNA via the FoundationACT assay if insufficient tumor is available for the FoundationOne assay) as outlined in the eligibility will be formally screened. Patients will receive 2 cycles of olaparib, as described on the TOPARP-A trial.[28] Patients will then be screened for progression by serum PSA. Progression will be defined as an increase of $\geq$ 25% in PSA from baseline. Patients without evidence of progression will receive a third cycle of treatment then undergo radical prostatectomy.

To assess response both PSA and Circulating tumor cells will be used. The primary assessment for response will be a reduction of at least 50% in the prostate-specific antigen level as utilized in the TOPARP-A trial. A secondary response assessment will be a reduction in the circulating tumor-cell count from 5 or more cells per 7.5 ml of blood to less than 5 cells per 7.5 ml as also utilized in the TOPARP-A trial. Circulating tumor-cell counts will be performed by CellSearch (Quest Diagnostics). Secondary efficacy assessments will also be based on pathologic assessments as described by Efstathiou et al and will include pathologic CR and pathologic stage of T2N0 versus > T2N0.[14] Since localized prostate cancer can be difficult to measure radiographically RECIST criteria will not be part of response assessment.

While high PSA responses (>90%) have been reported in studies of androgen deprivation therapies, these responses have not been associated a high degree of major pathologic response. For example in the study by Efstathiou et al, pathologic downstaging was reported in 32% and 50% of patients receiving LHRH + abiraterone + enzalutamide as compared to LHRH + abiraterone, respectively. The pathologic complete response rate was 0% and 2% respectively. Thus the primary response endpoint will be PSA response since this is objective, established and straightforward to measure. However, secondary assessments will also be important and based on pathologic criteria and reduction in circulating tumor cells. PSA progression-free survival will be an important assessment on the systemic effect of olaparib.

The primary objective of this proposal is to evaluate the response rate of neoadjuvant olaparib in patients who will be undergoing radical prostatectomy but are at very high risk for recurrence. Patients with germline or somatic alterations in DNA repair genes will be eligible. *The goal of this trial is to establish the activity of olaparib in the high-risk perioperative setting since recent phase III trials of perioperative*

*docetaxel and combination hormone therapies were negative leaving an open space for an active targeted agent such as olaparib.*

**3.0 PATIENT ELIGIBILITY: Source documentation certifying each inclusion and exclusion is required to be sent to BrUOG to certify eligibility.**

**3.1 Conditions for Patient Eligibility**

3.1.1 Biopsy confirmed adenocarcinoma of the prostate.

3.1.2 High risk for recurrence after prostatectomy including any of the following

- Lymph node involvement by radiographic criteria
- T3 or T4 disease by radiographic criteria
- T2 disease and either PSA $\geq$ 20 or Gleason 8,9 or 10

3.1.3 Mutations in any of the following DNA repair genes: BRCA1, BRCA 2, ATM, CHEK1, CHEK2, FANCONIS ANEMIA (FANCL), HDAC2, PALB2, BARD1, BRIP1, CDK12, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L, as detected by next generation sequencing performed on tumor specimen or circulating tumor DNA (ctDNA). Next generation sequencing must be confirmed by Foundation Medicine.

If prior testing has been completed, additional testing is not needed.

3.1.4 No prior chemotherapy or radiation for prostate cancer or PARP inhibitor. Prior and current hormone therapy (< 6 months from start date on study) for prostate cancer is allowed. Patients are allowed to remain on hormone therapy on study.

3.1.5 ECOG performance status 0-1.

3.1.6 Age$\geq$18.

3.1.7 Required entry laboratory parameters within 14 days of study registration

- ANC$\geq$ 1,500 cells/$mm^3$;
- Hemoglobin $\geq$ 10.0g/dL with no blood transfusion in the last 28 days
- Platelet count $\geq$100 x $10^9$/L,
- White blood cell > 3x$10^9$/L
- Total bilirubin $\leq$ 1.5 x ULN,
- AST and ALT $\leq$ 2.5 x ULN
    - Patients must have creatinine clearance estimated using the Cockcroft-Gault equation of $\geq$51 mL/min:

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

[a] where F=1 for males.

3.1.8 Life expectancy of at least 1 year as documented by treating physician.

3.1.9 All Men must be willing to consent to using a form of highly effective contraception while on treatment and for at least 4 months after last treatment on study

3.1.10 Signed study-specific consent form prior to study entry.

3.1.11 Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations- to be documented and submitted to BrUOG.

3.1.12 Patient agreed to not receiving any live virus and live bacterial vaccines while receiving study medication and during the 30 day follow up period.

3.1.13Patient agreed to not consume grapefruit juice while on study treatment.

**3.2 Exclusion Criteria**

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

3.2.1 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site or BrUOG)

3.2.2 Participation in another clinical study with an investigational anticancer product during the last 2 months (from day 1 of treatment on this trial).

3.2.3 Any previous treatment with PARP inhibitor for this or another cancer, including olaparib.

3.2.4 Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer or other solid tumors including lymphomas (without bone marrow involvement) which was curatively treated with no evidence of disease for ≥5 years from time of study registration. Diagnosis date and treatment confirmation required to be sent to BrUOG. Certification from treating physician that patient is disease free is required.

3.2.5 Resting ECG with QTc > 470 msec on 2 time-points within a 24 hour period or known family history of long QT syndrome

3.2.6 Patients receiving any systemic chemotherapy or radiotherapy within 3 weeks prior to study treatment. The last dose on antiandrogen hormone therapy must be > 72 hours prior to the first dose of olaparib.

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

3.2.8 Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort ) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. See section 4.3.1.3

3.2.9 Concomitant use of the substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp should be cautioned while on study. Documentation that this was explained to patient or document not applicable. See section 4.3.1.5.

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

3.2.10 Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) deemed related to previous cancer therapy, excluding alopecia.

3.2.11 Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML. To be certified by treating physician.

3.2.12 Patients with brain metastases. To be confirmed by treating physician. A scan to confirm the absence of brain metastases is not required unless the patient shows signs or symptoms deemed

concerning to the treating physician. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

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

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

3.2.15 Patients unable to swallow oral medications. Patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

3.2.16 Immunocompromised patients that according to treating investigator would increase their risk to protocol treatment, or Patients who are known to be HIV positive.

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

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

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

3.2.20 Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable as long as not within 28 days from study registration). If not applicable, document no prior transfusions.

3.2.21 Major medical or psychiatric illness which, in the investigator's opinion, would prevent completion of treatment and would interfere with follow-up.

3.2.22 History and/or confirmed pneumonitis. To be confirmed in writing.

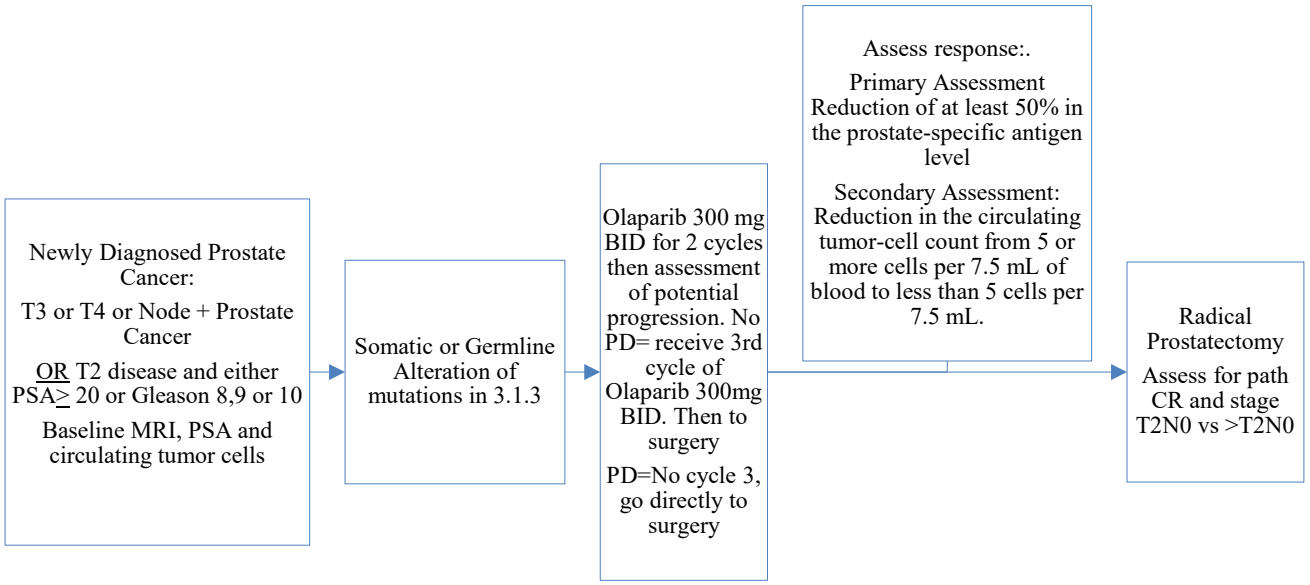
3.2.23 No distant visceral metastases.

**3.3 Re-Screening:**

Re-screening is defined in this protocol as screening a patient for this trial, once they have been found to not meet study eligibility criteria, outside of the 28-day screening window. While in the 28-day screening window, the patient may be screened multiple times (i.e. labs may be drawn and re-drawn), however, if a patient signs consent and then screen fails (does not meet the eligibility criteria) and the treating MD requests that the patient be re-screened outside of the 28 day screening window, sites are to contact BrUOG who will assess patients on a case by case basis. Depending on many diverse factors including the conditions that are being evaluated, the reasons why patient initially screen failed, and the nature of the initial results, re-screening may or may not be medically/scientifically appropriate. BrUOG should be made aware of such a situation with at least 72 hours and provided with information on screen-failure.

## 4.0 TREATMENT

### 4.1 Schema




**Patients will be followed for PSA progression free survival**

### 4.2 Olaparib:

**1 cycle = 4 weeks**

Dose: Olaparib 300 mg BID q 4 weeks +/- 3 days

All patients will receive 2 cycles of Olaparib. Post 2 cycles, patients will be assessed for progression by PSA. (Progression is defined as an increase of ≥ 25% in PSA from baseline).

If patients are found to progress they will be removed from study treatment and managed according to standard practice. If they have not been found to progress, a 3rd cycle of treatment will be administered prior to the patient going on to surgery.

There must be at least 21 days between the final dose of Olaparib and surgery (count the day after the last dose to the surgery date). Surgery is recommended > 21 days and less than 42 days from the last dose of olaparib.

**Patients should be instructed on the following each cycle:**

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 is 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.

**4.3 Prohibited and Restricted Therapies While Receiving Olaparib:**
**4.3.1 Medications that may NOT be administered unless otherwise noted**

**4.3.1.1 Other anti-cancer therapy:** 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. (Patients may have received up to 6 months of anti-androgen hormone therapy prior to entering the study.) The last dose on anti-androgen hormone therapy must be > 72 hours prior to the first dose of olaparib. Anti-androgen therapy must not be administered while receiving olaparib.)

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

***4.3.1.3 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. Patients requiring these medicines should be removed from study treatment.

***4.3.1.4 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.

***4.3.1.5:*** *Effect of olaparib on other drugs*

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

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

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

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine

- CYP1A2 – duloxetine, melatonin
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 -furosemide, methotrexate

#### 4.3.1.5 Grapefruit juice

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

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).

#### 4.3.1.6 Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully as per institutional practice 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 on the concomitant drug log

#### Contraception

Male patients with partners of child bearing potential, who are sexually active, must agree to the use of a form of highly effective contraception. This should be started from the signing of the informed consent and continue throughout period of taking study treatment and for 4 months after last dose of study drug.

## 5.0 TOXICITIES, DOSE MODIFICATIONS, AND MANAGEMENT

Toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using The National Cancer Institute's Common Toxicity Criteria (CTCAE) version 4.03 (Appendix C).

Dose Reductions for Toxicity deemed possibly related or related to olaparib

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

In order to begin a new cycle of treatment (day 1) the following criteria must be met:

- ANC≥ 1,500 cells/$mm^3$;
- Platelet count ≥100 x $10^9$/L,
- All treatment related non-heme toxicities must be ≤ grade 2 (including electrolyte imbalances)
- WBC ≥2,000$mm^3$
- **HGB ≥ 8 g/dl (if < 8 must improve to ≥ 10g/dl and then dose reduce)**
- Estimated CrCl ≥ 51ml/min. If < 51 ml/min: retest promptly and see "renal" section below

5.1 Dose Reductions for related Toxicity Requiring Dose Reductions (I and II):

**I. Patients developing the following treatment related toxicities at any time point during treatment (drug) are required to have olaparib held and not restarted until the toxicity resolves to grade 2 or less.**

- ANC <1000/$mm^3$ with fever or infection
- Grade 3 or 4 treatment related non-hematologic toxicities excluding alopecia. Grade 3 or 4 electrolyte abnormalities do not require a dose modification if the electrolyte disorder can be corrected to grade 2 or less within 72 hours. This must be documented and submitted to BrUOG.
- Delay of treatment for > 2 weeks due to toxicity.
- Estimated CrCl < 51 ml/min: retest promptly and see "renal" section below. If not taking patient off study then dose must be reduced.

Patients experiencing any of the above toxicities will be required to have a 1 dose level reduction of olaparib. Each patient can be dose reduced a total of 2 times. All dose reductions are permanent.

Patients requiring > 4 week dose delay for treatment related toxicities should be removed from protocol treatment.

**II. Patients experiencing the following toxicities, regardless of relationship, at any time point during treatment (drug), are required to have olaparib held and not re-started until resolution to grade 1 or less:**

- Grade 4 neutropenia (ANC < 500/$mm^3$)
- Grade 3 neutropenia (ANC< 1000/$mm^3$)
- Grade 3 thrombocytopenia (Platelets <50,000/$mm^3$-25,000)
- Grade 4 thrombocytopenia (Platelets <25,000/$mm^3$)
- Grade 3 leukopenia (WBC<2,000$mm^3$-1,000)
- Grade 4 leukopenia (WBC <1,000$mm^3$)
- Grade 3 anemia (HGB ≤ 8 g/dl) (must improve to ≥ 10g/dl)

Patients experiencing any of the above toxicities will be required to have a 1 dose level reduction of olaparib. Each patient can be dose reduced a total of 2 times. All dose reductions are permanent.

Study treatment should be discontinued if HGB, WBC, or PLT counts do not recover to CTCAE 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 to BrUOG and full reports must be provided by the investigator to BrUOG, who will then report all information to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

**Renal:**

If a patient's estimated calculated clearance falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly. A one level 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).
In instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

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

Patients requiring > 4 week dose delay for treatment related toxicities should be removed from protocol treatment.

Patients entered on the study who subsequently require strong or moderate CYP3A inhibitors should be removed from study treatments.

5.2 Modifications for Toxicity, Additional Considerations.

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions at the discretion of the treating physician and as per institutional standard practice.

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. BrUOG must be informed of all treatment interruptions with reason. 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.

### 5.2.1 Management of hematological toxicity

***Management of anemia***

**Table 4 Management of anemia**

| Hemoglobin | Action to be taken |
|---|---|
| **Hgb < 10** *but* **≥ 8 g/dl (CTCAE Grade 2)** | Give appropriate supportive treatment per institutional practice and investigate causality.<br>Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks.<br>If dose is interrupted:<br>If repeat Hb**< 10** *but* **≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hgb ≥ 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. |
| **Hgb < 8 g/dl (CTCAE Grade 3)** | Give appropriate supportive treatment (e.g. transfusion) and investigate causality.<br>Interrupt olaparib for a maximum of 4 weeks. until improved to Hgb ≥ 10 g/dl.<br>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 Hgb 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 5.2.1.1 for the management of this.

#### *5.2.1.1 Management of neutropenia, leukopenia and thrombocytopenia*

**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 CTCAE grade 3 or worse neutropenia, leukopenia or thrombocytopenia occurs.

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

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

***Management of prolonged hematological toxicities while on study treatment***

If a patient develops prolonged hematological toxicity such as:

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

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to CTCAE 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 to BrUOG and full reports must be provided by the investigator to BrUOG, who will then report all information to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

**Management of non-hematological toxicity**

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. 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. (see section 5.1)

***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.

***Management of nausea and vomiting***

Nausea was generally reported very early, with first onset within the first month of olaparib treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of olaparib treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients and can be managed by dose interruption, dose reduction and/or antiemetic therapy. Antiemetic prophylaxis is not required.

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

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

***Interruptions for intercurrent non-toxicity related events***

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with BrUOG.

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

If the patient requires a non-study related surgery or if they had a planned surgery- which would have had to be reported prior to enrollment, then study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

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.

**Overdose – See reference in section 11**

## 6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR *The day an assessment (PE, labs, scan etc) is completed is day 0 for counting for example labs drawn on Friday can be used for Monday dosing as this is within 3 days*

| Parameter | Pre-study, results and information to be sent prior to registration | Prior to each cycle dosing (-3 days of treatment) and approximately Every 2 weeks (mid-cycle) (+/- 3 days) while on olaparib [E] | 2 weeks after Olaparib completed (+7 day window) | 30 days post drug (+7 days) & 30 days post surgery completion (+ 7 day window) | Surgery 3-8 weeks post end of olaparib | FU[J] |
|---|---|---|---|---|---|---|
| Informed Consent (within 30 days of day 1) *pts are to be re-consented if ICF will be outside 30 day window | X | | | | | |
| History | X | | | | | |
| Physical examination | X | X | X[G] | | | |
| Weight | X | X | X | | | |
| Vital signs | X | X | X | | | |
| Toxicity Assessment | X | X | X[F] | X[F] | X[F] | |
| Concomitant medications | X | X | X | | | |
| Performance Status | X | X | X | | | |
| Biopsy or peripheral blood for assessment of abnormalities in DNA repair genes to Foundation Medicine[H] | Biopsy and/or peripheral blood to be taken from anytime pre study. Results required for registration | | | | | |
| Assessment of Circulating tumor cells [H] | 28 days prior to the start of treatment (results not required to register) | | X | | | |
| Operative report and pathology report from prostate surgery | | | | | X[C] | |
| CBC, diff, platelet count[E] | X (within 14 days) | X | X | | | |
| Na, K, BUN, Cr [DE] | X (within 14 days) | X | X | | | |
| Hepatitis B and Hepatitis C panel k | X (within 14 days of drug) | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| AST, ALT, Bili,[E] | X (within 14 days) | X | X | | | |
| INR | X (within 14 days) | As clinically indicated | | | | |
| PSA[E] | X (within 14 days of drug) | Week 8 (post-cycle 2 labs/pre-cycle 3) | X | | | X |
| UA | X (within 14 days of drug) | | | | | |
| MRI or CT pelvis[A] | X (within 56 days ) | As clinically indicated | | | | As clinically indicated |
| Bone scan[A] | X (within 56 days) | As clinically indicated | | | | As clinically indicated |
| Chest-xray [A] | X (within 56 days) | | | | | |
| 2 EKG[B] | X within 56 days | | | | | |
| Progression Free and overall Survival Disease status | | | | | | X |

[A]- Pelvic CT Scan or MRI, chest x-ray (chest CT may substitute) and bone scan for disease assessment to be performed within 56 days of study entry/registration. Report sent to BrUOG.. It is required that imaging that defined progression be sent to BrUOG as date of progression will be captured.

[B]- EKG within 56 days of study entry. Report to be sent to BrUOG at registration. Patient must have 2 EKGs within a 24 hour time period to certify patient does not meet exclusion 3.2.5

[C]- The operative note and pathology note will be sent to BrUOG. Documentation of post op complications to be submitted to BrUOG as well on AE log (if none, document "none" on AE log).

[D] CrCl to be calculated as well for required dose modification

[E] It is appropriate to use labs from screening for day 1, if labs are within 14 days. It is appropriate to use physical, weight, vitals, toxicity assessment, concomitant medication, performance status from screening for day 1 if within 14 days. All subsequent labs can be drawn within (-)3 days prior to day 1 of treatment of each week and +/- 3 days every 2 weeks while on study. One additional day is provided for a holiday. For PSA drawn week 8, this value is used to determine if a patient can continue on study for cycle 3 or if they must come off study drug treatment and go onto surgery.

[F] Adverse event evaluation will be done 2 weeks post treatment (drug) + 7 days and again with 30 days post last dose of study drug. A one week window is provided (+7 days). AE evaluation will be done again 30 days (+ 7 days) post surgery and this time point will capture surgical complications and delayed toxicities from the drug. This appointment is to occur with the treating physician or sub-investigator on the trial. SAEs and AESI will be captured through 30 days (+ 7 days) from the end of treatment (drug or surgery, whichever is last). SAEs and AESI occurring outside this 30 day window must be reported if the event is considered to be possibly related to the drug. BrUOG must be made aware of new treatment with start date.

[G] Physical exam to be done in coordination with 2 week AE assessment only (+ 7 day window), No physical exams are required post 2 week visit, but if one if completed at 30 days please submit to BrUOG.

[H] Biopsy for histologic confirmation of prostate cancer and assessment of DNA repair gene abnormality by Foundation Medicine can be performed anytime pre-study (diagnostic biopsy). Foundation Medicine final report to be sent to BrUOG in order to register patient. Peripheral blood analysis for circulating tumor cells should be performed with the use of CellSearch assay (Quest Diagnostics) and ordered as per institutional practice. The CTCs will be ordered even if at baseline the analysis is negative.

J BrUOG will be notified every 6 months (+/- 2 months) for 2 years the disease-free and overall survival status. Once patient is found to progress PSA is no longer required. If patient begins another treatment, the type of adjuvant treatment will be submitted to BrUOG.

k. HBsAg, AntiHBS, HepBcore, HCV antibody, HCV RNA

## 7.0 RESPONSE ASSESSMENT:

Primary Response Criteria

- Reduction of at least 50% in the prostate-specific antigen level from baseline will be considered a response.
- A 25% increase in PSA from baseline (registration) will be classified as disease progression.

Secondary Assessment of Response

- Reduction in the circulating tumor-cell count from 5 or more cells per 7.5 mL of blood to less than 5 cells per 7.5 mL. (CTCs will be determined by CellSearch assay through Quest Diagnostics)
- Pathologic complete response
- Pathologic stage of T2N0 versus > T2N0
- PSA progression-free survival.

Criteria for Disease Progression:

- First evidence of any lesion found on a scan suggesting metastatic disease (scans are to be done as clinically indicated)
- PSA progression: a 25% increase in the PSA level from baseline

## 8.0 PATIENT REGISTRATION

All patients will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form and the signed Patient Consent Form must be faxed to the BrUOG Central Office, Fax: (401) 863-3820 or emailed to BrUOG@brown.edu, at the time of registration and prior to patient treatment.

Details of patient's study participation should be documented in clinic/file notes. The Brown University Oncology Research Group will provide case report forms, included in the appendix, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms, flow sheets, off-study forms and follow-up forms should be mailed / faxed to:

**Brown University Oncology Research Group,**
**Brown University**
**Box G-R 001**
**Providence, RI 02912**
**Fax: 401-863-3820**
**Phone: 401-863-3000**
**BrUOG@brown.edu**

All support data must be sent in with the corresponding BrUOG forms. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must sign the off study form. Sites must confirm each element of inclusion and exclusion criteria and also provide support for all "pre-study" assessments on the schedule of evaluations table.

It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness.

## 9.0 PHARMACEUTICAL INFORMATION

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply olaparib to the investigator as oval tablets

Investigational product: Olaparib will be supplied as 100mg tablets, 150 mg tablets.

For all centers, 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 every 4 weeks (+/- 3 days) thereafter until the patient completes the study, withdraws from the study or closure of the study.

Study treatment is available as a tablet containing 100 or 150 mg of olaparib in 32 count bottles.

Patients will be administered olaparib orally twice daily.

### Dose Reductions

For guidance on dose reductions for management of AEs refer to section 5.0

Patients requiring strong or moderate CYP3A inhibitors are not eligible for the study ( 2 week wash-out is required). Patients entered on the study who subsequently require strong or moderate CYP3A inhibitors should be removed from study treatments.

### Renal Impairment

If subsequent to study entry and while still on study therapy, a patient's estimated calculated clearance. falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly. A one level 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 is it recommended that olaparib be discontinued.

### Labeling

Olaparib supply will be shipped unlabeled. Drug will be shipped through Fisher Clinical Services Depot.

A label will be found on the box that will contain the bottles inside. The bottles of drug will not be labeled themselves. The label on the box will outline part #, receiving #, Lot #, description (such as drug name) and quantity. Fisher Clinical uses the part # and receiving # as product identifiers.

It is required that upon receipt of drug shipment the pharmacy label both the boxes and bottles of Olaparib to include at the very least, a label noting:

- BrUOG 337

- For investigational use only
- Expiration date

**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.

**Ordering**

**Initial:**

- Following submission and approval of the required regulatory documents, BrUOG will share all approval documented with AstraZeneca and once confirmed by AstraZeneca and BrUOG, BrUOG will activate the participating hospital, which will allow for initial drug request.

All drug orders:

- There is no drug order form for this trial, the drug request must be sent to the following email addresses, requesting the number of initial bottles needed.
- It is required that the pharmacist confirm receipt of the requested drug shipment to the email addresses as well.
- The drug request email must be printed and saved in the BrUOG 337 pharmacy study binder, along with the shipment/packaging slip and confirmation of receipt email.
- All drug orders must be emailed to:
    - Gayle.Ewing@astrazeneca.com
    - cc to BrUOG@brown.edu

## 10.0 AGENT ACCOUNTABILITY

Investigational Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all olaparib using a Drug Accountability Record Form. Sites may utilize the NCI drug accountability form. Sites must track lot numbers, expiration dates, dosing dates and doses per patients and overall inventory. Sites must submit to BrUOG accountability logs during the study, at the end of the study and prior to destruction. To be able to destroy drug, sites must contact BrUOG who will obtain approval from Astra Zeneca prior to destruction. See section 15.5 as well

### 10.1 Treatment Compliance

Records of olaparib used, dosages administered, and intervals between visits will be recorded during the study.
Research staff are required to perform drug accountability prior to each new cycle of treatment to assess accountability and compliance for the prior cycle. Source documentation on the accountability is required to be kept as documentation in the patient's shadow chart in the research office at the treating hospital.

All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt drug preparation, and dispensing, including the applicable lot numbers. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

## 11.0 ADVERSE DRUG REACTION (ADR) REPORTING

***BrUOG considers the AE and SAE reporting period to begin when the subject signs the study specific informed consent.***

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of olaparib whether or not considered related to olaparib. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication.

### 11.1 Definitions

**An adverse event** is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

**Serious adverse event (SAE)**

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent **This must be documented and submitted to BrUOG**
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood

dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience**.**

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

**Adverse event of special interest= AESI**
**AESI = must be reported as a SAE even if not serious, using the important medical event choice**

**Unexpected adverse event**
An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

**Life-threatening**
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

### 11.2 Monitoring of Adverse Events and Period of Observation
Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

### 11.3 BRUOG ADVERSE EVENT REPORTING REQUIREMENTS
Investigators are required by Federal Regulation to report adverse drug reactions. Questions regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

Intensity for each adverse event will be scored using CTCAE Version 4.03. A copy of the CTCAE Version 4.03 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE Version 4.03. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

#### 11.3.1 Reporting
To ensure patient safety, every SAE and AE of special interest (AESI), regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study treatment (+7 days) (olaparib or surgery whichever occurs last), or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a

screen failure, whichever occurs first, must be reported by the site (within 5 business days of being made aware of the event) to BrUOG who will in turn report the SAE to AstraZeneca within 2 business days and up to 5 business days of being receipt of signed Medwatch 3500A from the site. Non-serious AEs are to be captured from time of consent until 30 days after the patient has stopped study treatment (+7 days) (olaparib or surgery whichever occurs last), or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first.
Any SAEs or AESIs experienced after this 30 day period (+7 days) should only be reported to BrUOG if the investigator suspects there may be a causal relationship to the study treatment (the study drug or surgery).

Information about all SAEs and AESIs are to be collected and recorded by the site (submitted to BrUOG) on the MedWatch 3500A and all applicable sections of the form will be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete MedWatch 3500A, within 5 business days of being made aware of the event and BrUOG will then send the completed 3500A form to AstraZeneca within 2 business days and up to 5 business days (from the time of BrUOG being in receipt of the signed site submitted Medwatch 3500A.

The original copy of the MedWatch 3500A and the email confirmation sheet must be kept with the case report form documentation at BrUOG. The email is: AEMailboxClinicalTrialTCS@astrazeneca.com

Follow-up information: The Medwatch 3500A must state that it is a follow-up to the previously reported SAE or AESI. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event. The follow-up information should describe whether the event has resolved or continues and whether the patient continued or withdrew from study participation. It is required that sites submit a follow-up SAE to report discharge from the hospital.

For Pharmacovigilance purposes and characterisation, any case of MDS/AML or new primary malignancy occurring after the 30 day toxicity follow up period (+7 days) should be reported to BrUOG via a SAE report (Medwatch 3500A) and BrUOG will report the event to AstraZeneca Patient Safety, whether it is considered a non-serious AE [eg non-melanoma skin cancer] or serious, 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. Any case of MDS/AML or any new primary meets AstraZeneca criteria to be reported as a SAE on this trial, even if this occurs more than 30 days post the last treatment (+7 days) **(olaparib or surgery, whatever is the last date).**

### 11.3.2. Pregnancy

**Paternal exposure**
Male patients should refrain from fathering a child or donating sperm during the study and for 4 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 4 months *after the last dose* should be followed up and documented.

**11.3.3 Expedited Reporting to AstraZeneca:**
Serious adverse events (SAE) are defined above. All SAE or AESI events must be reported, by FAX or email, to the Brown University Oncology Research Group who must inform AstraZeneca in writing using a Medwatch 3500A form (provided in a completed signed manner by the site), within 2 business days and up to 5 business days of receipt of completed final signed 3500A form. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE or AESI (such as discharge from hospital) is required. A copy of the fax transmission or email confirmation of the SAE report to AstraZeneca should be attached to the SAE or AESI and retained with the study records at BrUOG.

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. **All deaths during treatment or within 30 days following completion of active protocol therapy**(+7 days) **(olaparib or surgery, whatever is the last date), must be reported to BrUOG within 5 business days of the site being made aware of the event, or as soon as the investigator is made aware of the event. If the death is thought to be related to the study treatment (drug or surgery), deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event.**

Any serious adverse event or AESI occurring after the patient has provided informed consent and until 4 weeks (30 days (+7 days)) after the patient has stopped study participation/treatment (olaparib or surgery, whatever is the last date of treatment), or until the subject withdraws consent from study participation (declines participation) or at the time the patient becomes a screen failure, whichever occurs first, must be reported to BrUOG within 5 business days of the investigator being made aware of the event. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events and AESIs occurring more than 4 weeks (30 days (+7 days)) after study discontinuation (olaparib or surgery, whatever is the last date of treatment) need only be reported if a relationship to the study treatment (drug or surgery)

**11.4 Reporting requirements and procedures depend upon:**
1. Whether investigational agents are suspected of causing toxicity;
2. Whether the possibility of such a toxicity was reported in the protocol, consent form, or manufacturer's literature (Expected toxicity); and
3. The severity of grade of the toxicity.

**11.5 Assessing Causality:**
Investigators are required to assess whether there is a reasonable possibility that treatment caused or contributed to an adverse event. The following general guidance may be used:

**Yes:** if the temporal relationship of the clinical event to treatment administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

**No:** if the temporal relationship of the clinical event to treatment administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

**11.6 Types of Report: For sites:**
**Telephone report**: For SAE's and AESIs notification contact BrUOG Central Office (401) 863-3000 (or via email), immediately upon learning of the event (within 24 hours) and provide 24 hours before submitting the SAE for BrUOG planning (not applicable for SAEs and AESIs that require formal reporting within 24 hours of Investigator being made aware of event). For follow-up SAEs and AESIs please inform BrUOG within 24 hours and before sending in follow-up SAE reports.

**Written report**: Send the copy of the Medwatch 3500A form, within 5 business days of being made aware of the event to the BrUOG Central Office by email, scan or Fax:

Brown University Oncology Research Group
Phone: (401) 863-3000, Fax: (401) 863-3820
Emails: BrUOG@brown.edu

All deaths during treatment or within 30 days (+7 days) following completion of active protocol therapy (olaparib or surgery, whatever is the last date of treatment) must be reported within 5 business days of being made aware of the event or as soon as the investigator is made aware of the event. If the death is thought to be related to the study treatment (olaparib or surgery), deaths must be reported to BrUOG **within 24 hours** of the investigator being made aware of the event.

For Pharmacovigilance purposes and characterisation, any case of MDS/AML or new primary malignancy occurring after the 30 day (+7 days) toxicity follow up period should be reported to BrUOG via a SAE report (Medwatch 3500A) and BrUOG will report the event to AstraZeneca Patient Safety, whether it is considered a non-serious AE [eg non-melanoma skin cancer] or serious, 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. Any case of MDS/AML or any new primary meets AstraZeneca criteria to be reported as a SAE on this trial, even if this occurs more than 30 days (+7 days) post the last treatment **(olaparib or surgery, whatever is the last date).**

**11.6.1 Definition of Hy's Law (HL): See appendix F for complete information**

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

For potential HL 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.

Please refer to Appendix F on processes and procedures on how to manage and report such cases. For HL cases which are deemed SAEs, the same time frame for reporting is required (within 5 business days of being made aware of the event).

### 11.6.2 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*) and are to be reported as a SAE (important medical event). 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.

### 11.6.3 Olaparib adverse events of special interest

Adverse events of special interest [AESI] are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca (communication will be Investigator to BrUOG and BrUOG 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. AESIs will be reported to BrUOG in the same manner a SAE is and via a MedWatch 3500A, noting the event is an important medical event.

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

### 11.6.4 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. 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 will 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

**11.6.5 OVERDOSE**-To be reported by BrUOG to AstraZeneca regardless of the overdose meets SAE definition using the AstraZeneca Overdose form within 1 business day of being made aware of the event or obtaining confirmation of the overdose (there may be a situation when BrUOG is obtaining confirmation from the site to confirm an overdose has indeed occurred and BrUOG will wait to obtain confirmation prior to reporting the overdose). **Sites are required to review all cases of overdose and the treating physician is required to determine if the overdose also meets any SAE definition.** If so, the overdose must be reported as a SAE via SAE reporting requirements and time frames outlined in this protocol.

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). **If a patient takes 2 tablets at one time, or exceeds total daily dose of 600mg this will be considered an overdose and also a major deviation.**

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 on the CRF
- An overdose without associated symptoms is only reported on the Overdose AstraZenenca form (completed by BrUOG).

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca

**11.6.6 MedWatch 3500A Reporting Guidelines:**
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Patient number, initials, age, sex, weight
- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Lot number
- **Description of event, severity, treatment, and outcome, if known.**
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to investigational product and surgery and any other suspect medication and if the SAE is ***related to disease progression***, as determined by the principal investigator.
- **It is required that if non-serious events are included on the MedWatch, such as symptoms, that these be labeled as being non-serious, while the serious events be clearly labeled as being serious**
- **SAEs and AESIs must be typed**
- *It is required that the following are written on the Medwatch 3500A for tracking: BrUOG 337 & ESR-16-12357
- Must document current status of the patient (i.e. off study treatment, delayed cycle, coming off trial secondary to event etc)

**A final report to document SAE (such as discharge from hospital) is required.**

**Follow-up information:**
Additional Info maybe added to a previously submitted report by any of the following methods.

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

- At the time of follow-up submission site must submit laboratory information (admission, maximal, discharge), assessments/testing with results and AE log at a minimum.

Summarize new information and fax it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted. (The subject identifiers are important so that the new information is added to the correct initial report).
The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

**11.7 BrUOG Responsibility Regarding Reporting:**
The BrUOG Central Office will notify by email and/or fax all SAEs, regardless of relationship, to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than within 2 business days and up to 5 business days of receipt of completed final signed 3500A form (sent to BrUOG by the site). BrUOG will alert AstraZeneca to an SAE within 2 business days and up to 5 business days, of being made aware of the event via receipt of final signed Medwatch 3500A from the site. If the study has an IND, SAEs will be reported as an amendment to the IND and it will be sent to the division fax, within 5 calendar days of sponsor notification. If the study is IND exempt, the SAE will be sent within the same time frame, to the Medwatch fax line. A copy of the form will be kept by the BrUOG Central Office.

**Fax: 1-800-FDA-0178 (1-800-332-0178) For IND exempt study or for IND study the SAE will be sent to Center Drug Evaluation Division fax line that has responsibility for review of IND)**

**Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well**

**All SAEs will be faxed or emailed to: AstraZeneca**

**AZ SAE reporting:** email is: AEMailboxClinicalTrialTCS@astrazeneca.com ***or by fax to AstraZeneca's designated fax line:1-302-886-4114***

**11.8 Safety Reporting for IND Holders**
In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with following safety-reporting requirements:

**a. Expedited IND Safety Reports:**
**BrUOG will fax reports to the FDA for IND Safety Reports: 1 (800) FDA – 0178, unless per the IND status BrUOG is to submit the SAEs to the Division Fax instead.**

**b. IND Annual Reports, for IND study only**
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to olaparib as a supporter of this study.

**11.9 Adverse event updates/IND safety reports External**
AstraZeneca shall notify the Brown University Oncology Research Group (BrUOG) via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.

- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

BrUOG will then notify the sites who shall notify their IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects as per their local policies.

## 12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

Extraordinary medical circumstances or withdrawal of consent by the patient: If, at any time, the constraints of this protocol are detrimental to the patient's health, and/or the patient no longer wishes to continue protocol therapy, the patient shall be withdrawn from protocol therapy. Patients will also be withdrawn from study for the following reasons:

1. Disease Progression: Any patient with disease progression should be removed from study. Details and tumor measurements should be documented on flow sheets.
2. Patient is unable to tolerate the toxicity resulting from the study treatment, even with optimal supportive care, in the opinion of the Treating Physician. Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.
3. The physician feels it is in the best interest of the patient to stop the treatment.
4. Inter current illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
5. Non protocol chemotherapy or immunotherapy is administered during the study
6. Noncompliance with protocol or treatment—major violation
7. Patient is lost to follow-up
8. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)
9. Death
10. Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)

In this event notify:

**Brown University Oncology Research Group (BrUOG) Central Office,**
**Phone: (401) 863-3000**
**Fax: (401) 860-3820**

The BrUOG Central Office will in turn notify the Principal Investigator.

***Document the reason(s) for withdrawal on flow sheets. Follow the patient for survival with follow-up forms as dictated by the protocol**

## 13.0 FOLLOW-UP

All Subjects that discontinue treatment early for any reason (not including screen fails or patient with withdraw consent/decline study participation) as well as patients who complete therapy will be followed for survival (up to 2 years). At treatment discontinuation, subjects will undergo adverse event evaluation and again approximately 30 days (+7 days) post the last treatment with olaparib. In addition off study evaluations will be done when treatment is discontinued -Section 6.0.

## 14.0 REGULATORY CONSIDERATIONS

This research study is sponsored by the Principal Investigator, Dr. Anthony Mega, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. This study is financially supported by Astra Zeneca (the makers of olaparib).

### 14.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

### 14.2 Compliance with the Protocol and Protocol Revisions:

The study must be conducted as described in this approved protocol.

All revisions to the protocol must be created by the Brown University Oncology Research Group, and approved by AstraZeneca. The Investigator should not implement any deviation or change to the protocol without BrUOG's approval/favorable opinion by way of an approved exception. Any deviation to the trial which is not prior approved will be reviewed per the BrUOG SOP.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group.. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

### 14.3 Protocol amendments or changes in study conduct:

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed and approved and created by Brown University Oncology Research Group, who will obtain approval by Astra Zeneca and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Brown University Oncology Research Group, and Astra Zeneca.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Brown University Oncology Research Group and Astra Zeneca in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Brown University Oncology

Research Group and Astra Zeneca must be notified and the IRB at the center must be informed immediately.

## 15.0 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION

**15.1 Good Clinical Practice:** The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

**15.2 Patient Confidentiality:** In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Astra Zeneca or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

**15.3 Protocol Compliance:** The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Astra Zeneca and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Astra Zeneca and the regulatory authority (ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

**15.4 On-site Audits:** Regulatory authorities, the IEC/IRB and/or Astra Zeneca clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

**15.5 Drug Accountability:** Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient (patient initials, patient number and date of dosing), and disposal of the drug (if applicable and if approved through BrUOG by Astra Zeneca) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates, and patient numbers. The NCI DARF may be used for accountability.

All material containing olaparib will be treated and disposed of as hazardous waste in accordance with governing regulations and site's institutional practice.

**15.6 Premature Closure of the Study:** This study may be prematurely terminated, if in the opinion of the investigator or Astra Zeneca, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Astra Zeneca by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be returned to AstraZeneca.

**15.7 Record Retention:**

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principle Investigator (Anthony Mega, M.D.) and Brown University Oncology Research Group will monitor this study. The case report forms will be monitored against the submitted documents for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. Astra Zeneca will notify the Principle Investigator if an application is filed.

## 16.0 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.

- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

## 17.0 STATISTICS

The primary objective of this study is to estimate the response rate of neoadjuvant olaparib in patients with high risk prostate cancer. The primary assessment will be defined as a reduction of at least 50% in the prostate-specific antigen level prior to radical prostatectomy. We will differentiate between a 10% level of activity and a 40% level of activity. A response rate of 40% or higher would be clinically meaningful while a response rate of < 10% would not be worthy of further study.

Specifically, the hypothesis which will be tested is:

$H_{1:}\ p \leq 0.1$ versus $H_1: p \geq 0.4$

**Sample Size Calculation:**

Thirteen patients will be accrued to this study and evaluated for response as determined by the primary measure of 50% reduction in the PSA antigen level. A Simon two-stage design (Minimax) will be used in this study. The first 8 evaluable patients treated at the MTD will be assessed for response. The trial will be terminated early if 0 or 1 responses are observed in these patients. If at least 2 responses are observed, accrual will continue until a total of 13 evaluable patients are enrolled to the study. If 3 or fewer patients of 13 have a response, the null hypothesis will be accepted and it will be concluded that there is not sufficient activity to merit further investigation of the regimen. Otherwise, it will be concluded that the treatment regimen has sufficient activity to warrant further investigation. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 40%.

This study will provide the necessary preliminary data for consideration of a larger study in this population. The Brown University Oncology Research group has chosen to differentiate a 10% level of activity versus a 40% level of activity since a 30% difference of activity in this patient population with localized high risk prostate cancer would be clinically meaningful.

Methods:

Quantitative and qualitative variables will be expressed as medians (with range) and frequencies. Objective response rates will be calculated as relative rates with their 95% confidence interval (95% CI) limits. The median and two-sided 95% CIs for PFS will be estimated using the Kaplan-Meier method. Analysis will be performed using SPSS v.22.0 (IBM Corp., Armonk, NY, USA).

**Secondary Efficacy Analysis:**

Secondary end points include PSA progression-free survival (PFS), pathological complete remission (pCR) rate, pathologic stage of T2<0 versus > T2N0, and reduction in circulating tumor cells.

Progression will be defined as the following: time to radiographic progression, and/or time to PSA progression (a 25% increase in the PSA level).

PSA progression-free survival will be defined as alive without PSA progression.

**Feasibility:** The Brown University Oncology Research Group performed approximately 125 radical prostatectomies in 2015.

**18.0 REFERENCES:**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5. Rider JR, Sandin F, Andrén O, et al. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. Eur Urol 2013; 63:88–96.
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APPENDIX A **Agreement to Participate in a Research Study And Authorization for Use and Disclosure of Information**

**BrUOG 337: Olaparib Prior to Radical Prostatectomy For Patients with Locally Advanced Prostate Cancer and Defects in DNA Repair Genes**

You are being asked to take part in a research study. All research studies at <INSERT HOSPITAL NAME> hospitals follow the rules of the state of <INSERT STATE>, the United States government and <INSERT HOSPITAL NAME>. Before you decide whether to be in the study, you and the researcher will engage in the "informed consent" process. During this process, the researcher will explain the purpose of the study, how it will be carried out, and what you will be expected to do if you participate. The researcher will also explain the possible risks and benefits of being in the study, and will provide other information. You should feel free to ask any questions you might have. The purpose of these discussions is for you to decide whether participating in the study is the best decision for you.

If you decide to be in the study, you will be asked to sign and date this form in front of the person who explained the study to you. This form summarizes the information you discussed. You will be given a copy of this form to keep.

**Nature and Purpose of the Study**

Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. Anthony Mega, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. The study is financially supported by Astra Zeneca Pharmaceuticals, the makers of the drug olaparib

You are being asked to take part in this study because you have prostate cancer. Your cancer has not spread to other organs in your body and may be removable by surgery (radical prostatectomy). However the chance your prostate cancer will grow back in 5-10 years is approximately 40-75%. (Forty to 75 patients out of 100 with prostate cancer similar to yours will have a recurrence of their cancer.) Your doctor will discuss your cancer with you and review the risk of your cancer recurring based on the features of your cancer.

This study will evaluate approximately 3 months of treatment with the drug olaparib in patients with prostate cancer. A capsule formulation of olaparib (tradename Lynparza™) is approved by the United States Food and Drug Administration (FDA) for the treatment of women with certain types of ovarian cancer and breast cancer. Olaparib is an investigational drug in prostate cancer, which means it is not approved by the FDA for treatment of prostate cancer. A tablet formulation of olaparib is being tested in this study. It is a new formulation which is more convenient for patients than the approved capsule formulation because fewer tablets of olaparib need to be taken daily than with capsules.

Olaparib is called a PARP inhibitor. PARP inhibitors may be helpful in cancers that have "defects in DNA repair genes". This means that the function of the DNA is not working the way it should because the repair gene is defected, which can lead to an increased risk in cancer. Approximately 1 in 5 patients with prostate cancer (20%) have cancers that have defects in DNA repair genes. In a previous study of patients with advanced prostate cancer with defects in DNA repair genes whose cancer had spread to other organs (a more progressed cancer then you have), olaparib caused cancer reduction in 14 of 16 (88%) patients. Some of the mutations found are going to be germline (inherited) and some will be

somatic (found only in the cancer cells). If it is found that the detected mutation is more likely germline (inherited), you have the option of also being referred for genetics consultation and additional testing. Please speak with your doctor about this.

The purpose of the study is to evaluate whether olaparib can reduce prostate cancer with defects in DNA repair genes when olaparib is given for approximately 3 months before surgery.

We expect to enroll approximately 13 patients into this study.

**Explanation of Procedures**

**Determination if your cancer has a defect in a DNA repair gene.**
Your tumor tissue will be assessed by Foundation Medicine, a laboratory in Cambridge MA, to determine if your cancer has a defect in a DNA repair gene. If your cancer does not have a defect in a DNA repair gene, then you will not be able to receive treatment on this clinical study and your doctor will discuss with you what options are best for you. If your tumor tissue has not already been examined by Foundation Medicine then your doctor will send it out as part of your standard cancer assessment.

**What will happen if I take part in this research study?**

If you take part in this study, and your tumor tissue is found to have a defect in a DNA repair gene, and you choose to take part, you will have the exams, tests and procedures to show that you can be in the study and while on study. They are part of regular cancer care.

**Baseline tests prior to starting treatment:**

- Medical history
- Physical examination, including weight, vitals, performance status, toxicity assessment, demographics, concomitant medications (to document what other medications, if any you take)
- Blood tests - approximately 3 tablespoons of blood. These blood tests will evaluate your blood counts, kidney and liver function and whether you previously or have hepatitis. A prostate specific antigen (PSA) test will also be run.
- About 3 tablespoons of blood will be sent to a commercial laboratory (Quest Diagnostics) to try to count the number of prostate cancer cells that can be detected in your bloodstream
- MRI or CT scan of the pelvis
- Bone scan (to be sure your cancer hasn't spread to your bones)
- Chest imaging
- EKG.

**Tests while you receive study treatment with olaparib:**
- Physical examination, including weight, vitals, performance status, toxicity assessment, review of other medications you may be taking, approximately every 2 weeks.
- Blood tests, approximately 3 tablespoons of blood, every 2 weeks.
- Your PSA will be repeated after 2 months of olaparib to try to determine if the olaparib is helpful in treating your cancer.

**Treatment- Olaparib:**
All patients will receive 2 cycles of treatment. A cycle is considered 4 weeks. You will take two doses of olaparib at approximately the same time each day, morning and evening, approximately 12 hours apart, for 2 months. After 2 cycles of treatment you will have a blood test, approximately 3 tablespoons and

your doctors will assess if the olaparib is helping to treat your prostate cancer by checking the PSA blood test. As long as the PSA is not increasing you will receive 1 additional cycle of olaparib to complete 3 cycles (months) of treatment.

- Olaparib tablets should be swallowed with one glass of water, with or without food.
- The tablets should be swallowed whole and not chewed, crushed, dissolved or divided.
- If vomiting occurs shortly after the study drug tablets are swallowed, the dose should **only** be replaced if you are able to clearly see all of the intact tablets and you can count all tablets
- Should you miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), you 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 you should take your next dose at the next scheduled time.
- You should also not drink grapefruit juice as this can affect the way the study medication works.

It is possible that your olaparib could affect your other medication. There are certain medications that you will **not** be allowed to take with the study medication during the study including other anti-cancer therapies and certain vaccines. Your study doctor will discuss a list of medications that you must avoid while you are taking your study medication so it is important to consult them before taking anything new.

Once you complete the study treatment with olaparib, you will have a study visit. During this visit the following will occur:

- Physical examination, including weight, vitals, performance status, toxicity assessment, concomitant medications (to document what other medications, if any you take)
- Blood tests, approximately 3 tablespoons of blood
- After you have completed treatment, about 3 tablespoons of your blood will be sent to Quest Diagnostics to try to count the number of prostate cancer cells that can be detected in your bloodstream to compare this to the number of prostate cancer cells detected in your blood before starting olaparib.
- You will also undergo a toxicity assessment, physical, performance status assessment approximately 30 days after your last treatment with olaparib

**Surgery:**

3-8 weeks after completion of olaparib you will have surgery to remove your prostate cancer.
By enrolling in this trial, you understand that you are delaying surgery for your high-risk localized disease.

**Follow-up:**

After surgery, you will see your study doctor approximately every 4 months for 2 years. During that time the following will occur:

- Blood PSA (about a tablespoon of blood) until you are found to progress.
- Survival and disease status

## How long will I be in the study?

You will receive olaparib for approximately 3 months. Then you will have surgery 3-8 weeks after completing olaparib. Afterwards you will be followed for cancer recurrence every 4 months for approximately 2 years. Total study involvement is about 2.5 years.

**Can I stop being in the study?**

Yes. You can decide to stop at any time. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be evaluated. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

**Costs for participating in this study**

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these 'research only' services include the following:

- You will receive the drug olaparib at no charge as it is being provided at no cost by AstraZeneca, the maker of the drug.
- The analysis to determine if your cancer has a defect in the DNA repair genes
- Evaluation of your blood for circulating tumor cells before receiving olaparib and after you have completed olaparib.

Other services you will receive during this research study are considered "routine clinical services" that you would have received even if you were not in the research study. Examples are; all study doctor visits, blood tests, PSA test, drugs used to reduce side effects from olaparib, MRIs, EKG, chest x-ray and CT scans and bone scans. These services will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

**Contact Information:** If you have any questions regarding this study, you may contact your site Principal Investigator, Anthony Mega, 401-444-3234.

**Discomforts and Risks**

You may have side effects while on this study. We will monitor everyone in the study for any side effects. Contact your study doctor if you experience a side effect or have any questions about possible side effects.

## OLAPARIB

Side effects may be mild or serious. We may give you medicines to help lessen side effects. Some side effects will go away as soon as you stop taking the drug. In some cases, side effects can be serious, long-lasting, or may never go away. Taking part in this study may lead to time away from work.

**Tell your doctor straight away if you notice any of the following side effects – you may need urgent treatment:**

**Very common side effects > 10% :**

- Feeling sick (nausea)
- Being sick (vomiting)
- Tiredness/weakness
- Indigestion/heartburn (dyspepsia)
- Loss of appetite
- Headache
- Change in taste of foods (dysgeusia)
- Dizziness
- Diarrhea. Your doctor may prescribe a medicine to treat this. If it gets severe, tell your doctor straight away.
- Decrease in the number of red blood cells (anemia) which can be associated with symptoms of shortness of breath, fatigue, pale skin or fast heart beat
- Decrease in the number of white blood cells that support the immune system (lymphopenia) which can be associated with increased susceptibility to infection
- Increase in blood creatinine seen from a laboratory test showing how your kidneys are working.
- Cough
- Constipation
- Abdominal and back pain
- Fever
- Anorexia/decreased appetite
- Dyspnea (shortness of breath)
- Reduced number of neutrophils in the blood (a type of white blood cell), leading to increased chance of infection
- Decrease in the number of platelets in blood (thrombocytopenia) which can be associated with symptoms of bruising or bleeding for longer if injured
- Decrease in the total number of white blood cells (leukopenia) and in certain white blood cells (neutropenia) that protect from infection, which can be associated with symptoms of fever
- Joint pain
- Pain in the stomach area under the ribs (upper abdominal pain)

**Common side effects: 1-10%**

- Sore mouth (stomatitis)
- Rash
- Reduced platelets which can cause bleeding

**Uncommon side effects that may occur are: <1%**

- Allergic reactions
- Itchy rash on swollen, reddened skin (dermatitis)
- Mean cell volume elevation (an increase in size of red blood cells): This will be monitored by the laboratory safety tests that will be done in this study because this doesn't normally have any symptoms.

**Driving and using machines:** The study drug may affect your ability to drive or use machines. If you feel dizzy, weak, or tired while taking your study treatment, take special care when driving or using tools or machines.

**Other potential risks:**

Other side effects have been seen in previous studies, but it is not yet known if these were related to olaparib, or if they were unrelated events possibly due to the patient's cancer or other cause. Assessing the full range of side effects of olaparib is an important part of this study.

**Pneumonitis** (lung inflammation) has been reported in a small number of patients treated with olaparib in previous studies, and some reports have been fatal. It is not known if olaparib caused the pneumonitis in these patients as they had other possible causes such as lung cancer and/or metastases in the lungs, pre-existing lung disease, were smokers, or had been treated previously with chemotherapy or radiotherapy. If you experience any new or worsening symptoms of shortness of breath, cough and fever, you should contact your Study Doctor as soon as you can.

**Myelodysplastic syndrome and acute myeloid leukemia:** These side effects have been reported in a small number of patients treated with olaparib in previous studies and the majority of cases have been fatal. It is not known if olaparib caused myelodysplastic syndrome and/or acute myeloid leukemia in these patients as they had other possible causes, in particular they had received extensive previous chemotherapy. Your Study Doctor will monitor your blood cell levels during the study and may decide you need to have further tests, which may include a bone marrow sample or a blood sample.

- Myelodysplastic syndrome is a pre-cancerous condition where the bone marrow isn't as good at producing blood cells as it was before (red blood cells and/or white blood cells and/or platelets). This condition has the potential to transform into acute myeloid leukaemia

- Acute myeloid leukaemia is a cancer of the bone marrow where many abnormal and immature white blood cells (blast cells) are made while normal functioning blood cells are not made.

The Study Doctor may decide to interrupt and/or reduce your olaparib dose if you experience certain side effects. If your dose is reduced you will be given a new bottle of tablets.

**<u>Male patients</u>**

The study drug may harm the unborn child. Tell your study doctor immediately if your partner becomes pregnant while taking study treatment or within 4 months after your last dose of study treatment.

While taking the study drug, and for 4 months after stopping treatment, you must use a condom when having sexual intercourse with a female partner, even if they are pregnant. Your female partner must also use a suitable method of contraception. You must not donate sperm while taking study treatment and for 4 months after the last dose of study treatment.

**By signing this document you are acknowledging that you understand and agree to the information presented in this reproductive risk section.**

**Surgery:**

Surgery to remove your prostate (prostatectomy) is a standard operation for prostate cancer. You will be given a separate consent form to review and sign prior to that surgery. That consent form will review the standard risks associated with the surgery.

By participating in this study, you agree to delay your surgery by up to 3 months to receive the drug. Your doctors are studying olaparib before surgery to learn if olaparib can reduce the risk that your cancer may recur after surgery. However, if olaparib is not effective, this may leave you at a higher risk of metastasis (cancer spreading to other places in the body), death, and disability.

**Antiemetics (anti-nausea medications):** Various medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction.

You will receive pre-medication to reduce the risk of infusion/injection reactions on your treatment days. Overall, the pre-medications you will be given are well tolerated.

**Venipuncture** (inserting a needle into a vein to obtain blood or give medication): May cause inflammation, pain, bruising, bleeding, or infection.

In order to monitor the side effects, your physician will examine you frequently and obtain laboratory tests to determine the effects of your treatment and alter the drug dosages if necessary.

**Risk of MRI imaging:**

Rarely MRI has been associated with kidney damage.

Your doctors will be carefully monitoring your condition to minimize any possible risks to you. If your doctors feel that the side effects are too severe in your particular case, they will lower the dose of the medications or even stop them.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

**Benefits**

The goal of this study is to determine if olaparib can reduce the size of prostate cancers that have defects in DNA repair genes when administered for 3 months prior to radical prostatectomy. The treatment may not be effective and may not help in treating your cancer.

We do know that the information from this study will help doctors learn more about this drug as a treatment for cancer. This information could help future cancer patients.

**Alternative Therapies**

What other choices do I have if I do not take part in this study?

- Having surgery for prostate cancer
- Having hormone therapy for prostate cancer
- Having radiation therapy for prostate cancer
- Having no treatment and just being observed.

Talk to your doctor about your choices before you decide if you will take part in this study.

**Refusal/Withdrawal**

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

If you decide to withdraw from this study (stop taking study medication) for any reason, you will be asked to sign a form indicating whether you give your permission for your doctor and the research staff to continue to collect and submit follow-up information on your health status from your physicians and medical record. After signing the form, you still have the right to change your mind, at any time, regarding follow-up after withdrawal.

**Medical Treatment/Payment in Case of Injury**

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Neither Dr. Anthony Mega, the sponsor of the study, nor BrUOG, the coordinating center, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

**Rights and Complaints**

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies you may contact<INSERT NAME> in the <INSERT HOSPITAL NAME> Office of Research Administration, at <INSERT CONTACT>

**Confidentiality**

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies/ might use, release, or receive such information:

- The researcher and their support staff;
- The study sponsor Dr. Anthony Mega, BrUOG, the group coordinating the study and their affiliates, and Astra Zeneca, the supplier of olaparib, and financial supporter of this trial and their authorized agents
- Doctors, nurses, laboratories and others who provide services to you or the sponsor in connection with this study;
- The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights; Governmental agencies in other countries where the study drug may be considered for approval
- People who volunteer to be patient advocates or research volunteer protectors;
- Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.
- Accrediting Organizations

The results of this research study and any correlative studies, in which you agree to participate, will probably be shared with other people and may be published in scientific reports, but your name and the fact that you were in this study will be kept confidential. Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality.

There are times when the law might require or permit <INSERT HOSPITAL NAME> to release your health information without your permission. For example, <INSERT STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no affect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL NAME> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.
Additionally, a description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
For more detail about your privacy rights see the <INSERT HOSPITAL NAME> Joint Privacy Notice which has or will be given to you.

**GINA STATEMENT**

This study involves 'genetic testing' as defined by the Genetic Information Nondiscrimination Act of 2008 (GINA). GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. There are some limitations to GINA's protections (it does not apply to all insurers or employers, nor does it apply to all genetic information, such as information related to a genetic disease that you already have). In addition to GINA's protections regarding the ultimate use to which your genetic information is put, Lifespan's privacy policies generally protect the privacy of such information and restrict its release outside of Lifespan, unless you specifically authorize its disclosure or unless disclosure without your authorization is permitted under applicable privacy laws.

**SIGNATURE**

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the <INSERT HOSPITAL NAME> Privacy Notice*

**This informed consent document expires on _____.**

**The Researcher is required to provide a copy of this consent to you.**

_____ _____ _____
Signature of study volunteer/authorized representative* Date and Time when signed

I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

_____ _____
Signature of witness (required if consent is presented orally or at the request of the IRB) Date

_____ _____
Signature of Translator Date

_____ _____ _____
Signature of researcher or designate Date and Time when signed

* If signed by agent other than study volunteer, please explain below.

_____

_____

APPENDIX B: Checklist

**BrUOG 337: Olaparib Prior to Radical Prostatectomy For Patients with Locally Advanced Prostate Cancer and Defects in DNA Repair Genes**

**Inclusion Criteria**

_____(y/n) Histologically confirmed adenocarcinoma of the prostate

_____(y/n) No prior chemotherapy for advanced prostate cancer or PARP inhibitor. Prior and current hormone therapy (< 6 months) for prostate cancer is allowed.

_____(y/n) High risk for recurrence after prostatectomy including any of the following

- Lymph node involvement by radiographic criteria
- T3 or T4 disease by radiographic criteria
- T2 disease and either PSA ≥ 20 or Gleason 8,9 or 10

_____(y/n) Defects in any of the genes noted in section 3.1.3, document on "on study" form and submit results

_____(y/n) No distant visceral metastases.

_____(y/n) Voluntary, signed written informed consent, Date signed_____

_____(y/n) Age ≥18

_____(y/n) Must be willing to consent to use effective contraception while on treatment and for at least 4 months afterwards

_____(y/n) Bone scan, MRI or CT of the pelvis, and chest X-ray completed per section 6

_____(y/n) EKG per section 6 at study entry and resting ECG with QTc > 470 ms.

_____(y/n) Life expectancy at least 1 year as noted by treating investigator

_____(y/n) Absolute neutrophil count ≥ 1,500/ul, Date_____

_____(y/n) Platelet ≥ 100,000/uL, Date_____

_____(y/n) Total bilirubin ≤1. 5 x ULN, Date_____

_____(y/n) AST≤ 2.5x ULN and ALT ≤ 2.5x ULN Institution

_____(y/n) Creatinine clearance ≥ 51 mL/min

_____(y/n) HGB ≥ 10.0g/dL with no blood transfusión in last 28 days

_____(y/n) WBC > 3x $10^9$/L

_____(y/n) ECOG PS 0-1

_____(y/n) Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations

_____(y/n) Patient agreed to not consume grapefruit juice while on study treatment. Submit documentation patient was instructed and agreed.

_____(y/n) Patient agreed to not receive any live virus and live bacterial vaccines while receiving study medication and during the 30 day follow up period. Patient should be made aware of this

**Exclusion Criteria**:

_____(y/n) Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site or BrUOG)

_____(y/n) Participation in another clinical study with an investigational anticancer product during the last 2 months (from day 1 of treatment on this trial).

_____(y/n) Any previous treatment with PARP inhibitor for this or another cancer, including olaparib.

_____(y/n) Other malignancy in the last 5 years except adequately treated non-melanoma skin cancer or other solid tumors including lymphomas (without bone marrow involvement) which was curatively treated with no evidence of disease for ≥5 years from registration.

_____(y/n) Resting ECG with QTc > 470 msec see section 3.2.5

_____(y/n) Known family history of long QT syndrome

_____(y/n) Patients receiving any systemic chemotherapy or radiotherapy within 3 weeks prior to study treatment

_____(y/n) The last dose on antiandrogen hormone therapy must be > 72 hours prior to the first dose of olaparib.

_____(y/n) Receiving strong or moderate CYP3A inhibitors

_____(y/n) Receiving strong or moderate CYP3A inducers

_____(y/n) Concomitant use of the substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp should be cautioned while on study.

_____(y/n) Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) deemed related to previous cancer therapy, excluding alopecia.

_____(y/n) Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML.

_____(y/n) Patients with brain metastases.

_____(y/n) Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any prior major surgery.

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

_____(y/n) Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

_____(y/n) Patients who are known to be HIV positive or who are immunocompromised- see section 3.2.16

_____(y/n) Patients with a known hypersensitivity to olaparib or any of the excipients of the product.

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

_____(y/n) Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)

_____(y/n) Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable as long as not within 28 days from study registration)

_____(y/n) Major medical or psychiatric illness which, in the investigator's opinion, would prevent completion of treatment and would interfere with follow-up.

_____(y/n) History and/or confirmed pneumonitis

_____(y/n) Visceral metastases

The support documentation, per the requirements under the study parameters section of this study, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

1) Eligibility Form Enclosed __Not Enclosed _____ Not Applicable __

2) Heme/Onc initial note Enclosed __Not Enclosed _____ Not Applicable __

3) Pathology Report(s) Enclosed __Not Enclosed _____ Not Applicable __

4) MRI/CT Report(s) Enclosed __Not Enclosed _____ Not Applicable __

5) Lab Source Document Enclosed __Not Enclosed _____ Not Applicable __

6) ICF signature page

7) Other documents, please list_____

IRB approval date of protocol: _____

Hospital where patient will be treated with Oncologist: _____

Date patient will begin treatment: _____ Primary Physician: _____

Your signature: _____

**APPENDIX C**

**NCI CTC Version 4**

Toxicity will be scored using NCI CTC Version 4 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4can be downloaded from the CTEP homepage: (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4

**APPENDIX D**

ECOG PATIENT PERFORMANCE STATUS

| STATUS | KARNOFSKY | ZUBROD-ECOG-WHO | Description |
|---|---|---|---|
| No complaints | 100 | 0 | Normal activity |
| Able to carry on normal activities | 90 | 1 | Symptoms, but fully ambulatory |
| Normal activity with effort | 80 | | |
| Cares for self. Unable to carry on normal activity or to do active work | 70 | 2 | Symptomatic, but in bed <50% of the day |
| Requires occasional assistance, but able to care for most of his needs | 60 | | |
| Requires considerable assistance and frequent medical care | 50 | 3 | Needs to be in bed >50% of the day, but not bedridden |
| Disabled, requires special care and assistance | 40 | | |
| Severely disabled. Hospitalization | 30 | 4 | Unable to get out of bed |

| | | | |
|---|---|---|---|
| indicated though death non imminent | | | |
| Very sick. Hospitalization<br><br>Necessary. Active support treatment necessary | 20 | | |
| Moribund | 10 | | |
| Dead | 0 | | |

From: Minna J.D., Higgins G.A and Glapstein E.J. Cancer of the lung: In: DeVita V, Hellman S., Rosenberg S., (Eds.). Cancer: Principles and Practice of Oncology, Lippincott, Philadelphia, 1984, p. 536

**APPENDIX E**

CASE REPORT FORMS

Attached separately are the BrUOG Case Report Forms

**APPENDIX F:**

**HY'S LAW 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.

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).**

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

**For Studies using local laboratories:**

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

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

**Follow-up**

*Potential Hy's Law* ***Criteria not met***

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

*Potential Hy's Law Criteria* ***met***

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See **Error! Reference source not found.**
- Notify the AstraZeneca representative (contact BrUOG who will contact the company)

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 CRF
- 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. (this communication will be organized by BrUOG)

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 and report the SAE according to section 11

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 SAE processes in section 11

  - 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

**Actions Required for Repeat Episodes of Potential Hy's Law**

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease

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

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

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

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

**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