Academic and Community Cancer Research United (ACCRU)

A Phase II Study of Olaparib in Patients with Advanced Biliary Tract Cancer with Aberrant DNA Repair Gene Mutations

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site

[redacted]

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Correlative Science Co-Chair: [redacted]

Statistician: [redacted]

Drug Availability
Drug Company Supplied: Olaparib (IND Exempt)

√ Study contributor(s) not responsible for patient care.

Research Coordinating Center

[redacted]

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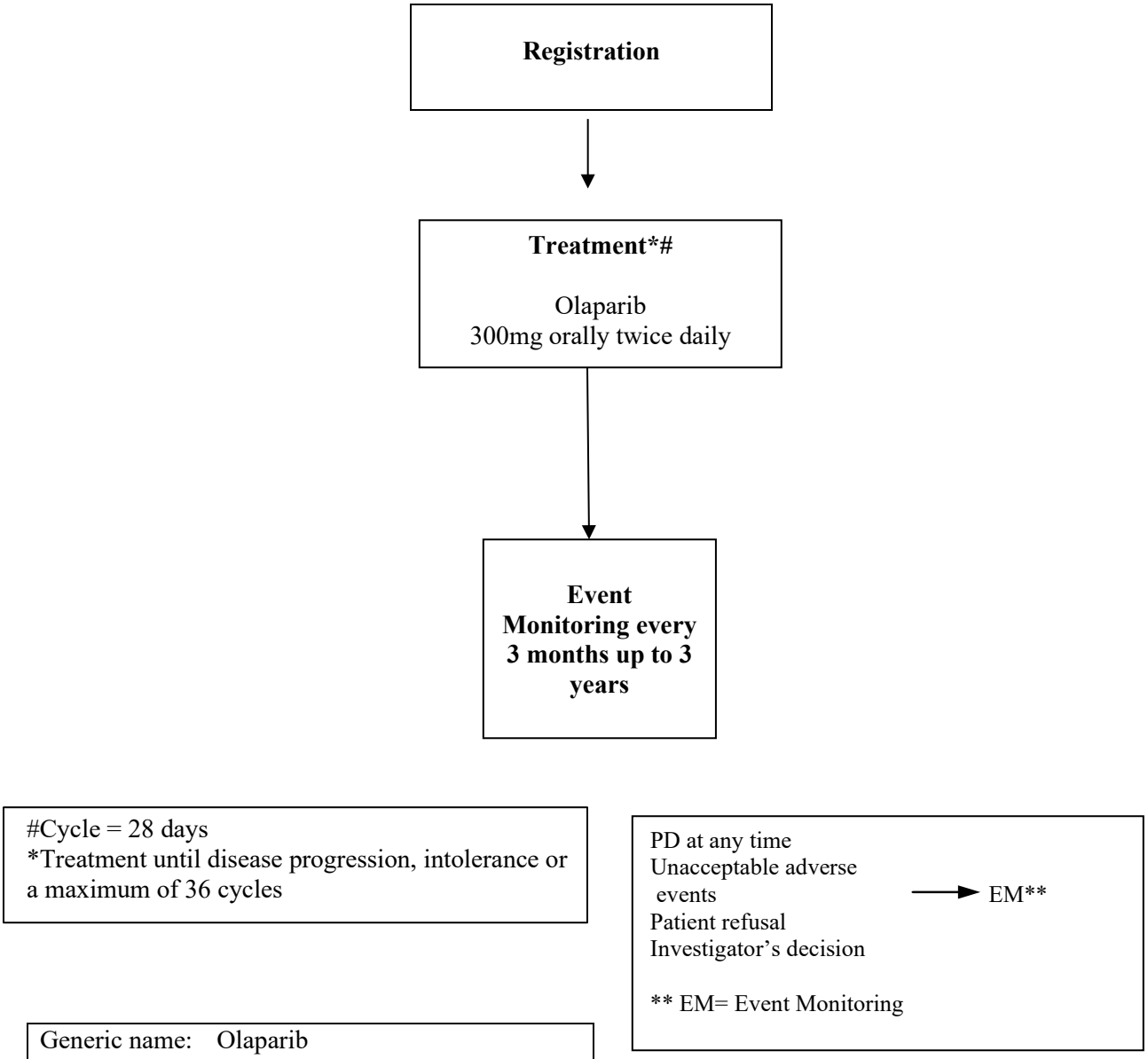
Index

Schema


Registration
Treatment*#
Olaparib
300mg orally twice daily
Event Monitoring every 3 months up to 3 years
#Cycle = 28 days
*Treatment until disease progression, intolerance or a maximum of 36 cycles
PD at any time
Unacceptable adverse events
Patient refusal
Investigator's decision
EM**
** EM= Event Monitoring
Generic name: Olaparib
Brand name(s): Lynparza
Availability: McKesson

1.0 Background

1.1 Biliary cancers (BTC) are a group of rare chemo resistant tumors with one of the worst prognosis among gastrointestinal malignancies.[1]

Most patients present with advanced disease at the time of diagnosis where the standard treatment for untreated BTC is the combination of platinum based chemotherapy. The response to GP is heterogeneous, with varying duration of response.[2] Although the majority of patients (>80%) experience disease control with GP, certain patients are resistant to GP therapy and progress rapidly. [3,4] However a subset of patients are deemed to be platinum sensitive and receive durable and meaningful responses to platinum based chemotherapy. Genomic profiling studies in solid tumor malignancies, including biliary tract cancer have shown that a significant proportion of BTC express loss of function mutations in genes associated with DNA repair.[5-7] These constitute up to 20% of BTC patients, with a higher proportion identified in those with extrahepatic cholangiocarcinoma. This is the highest proportion of DNA repair mutations seen in any gastrointestinal cancer. These genes include, but are not limited to: *ATM, ATR, BRCA 1/2, RAD51, PALB2, PTEN, FANC, NBN, EMSY, MRE11, ARID1A.* Thus, patients whose tumors express loss of function of genes associated with DNA repair, or homologous recombinant repair **(HRR)**, potentially may benefit most from agents aimed against DNA repair mechanisms.

1.2 Role of PARP in DNA repair

The PARP family of proteins is comprised of 17 members that catalyse poly (ADP-ribosyl) ation of proteins by promoting the synthesis and transfer of negatively charged ADP-ribose polyes.[8-10] Although PARP1 is involved in a diverse range of cellular processes, its major role is in DNA repair. PARP1 is the predominant isoform of the PARP family, accounting for up to 80% of PARP activity.[11] PARP2, which exhibits a high degree of structural similarity to PARP1, is also able to promote PARP activity, especially in the absence of PARP1.[12,13] PARP1 & PARP2 are the only members of the PARP family known to be involved in DNA repair.[14-17] Binding to DNA strand interruptions stimulate the catalyitic activity of PARP1 and PARP2 leading to poly (ADP-ribosy)lation of key DNA repair proteins.[15]

1.3 Synthetic lethality of PARP inhibition in HRD cancer cells

In order to combat the detrimental effects of DNA damage, mammalian cells have evolved a complex network of interconnected pathways, proteins known as the DNA damage response (DDR). Homologous recombinant repair (HRR) and non-homologous end joining are the two major pathways involved in the repair of double strand breaks in eukaryotic cells.[18-21] Two DNA repair proteins with a pivotal role in HRR are BRCA1 and BRCA2. Importantly, there is substantial pre-clinical and clinical evidence demonstrating sensitivity of BRCA1 and BRCA2 deficient cancers to PARP1/2 inhibition. In 2005, two landmark pre-clinical studies showed that PARP1/2 inhibitors have profound activity in cancer cells without functional BRCA1 or BRCA2.[22,23] In subsequent phase I and II trials, PARP1/2 inhibitors were highly active in ovarian, breast and prostate cancers with germline BRCA inactivating mutations.[24-28] The potency of PARP 1/2 inhibitors in BRCA-deficient cells arises from a synthetic lethality, where the combination of multiple genomic alterations result in cellular death.[29] PARP1/2 inhibition suppresses base excision repair and results in the accumulation of single-strand breaks (SSBs). In turn, SSBs result in

replication fork stalling and collapse that result in the formation of double strand breaks during DNA replication.[30,31] In cells that express homologous recombinant deficiency (HRD), these double strand breaks are either repaired by non-homologous end joining pathway or are left unrepaired, leading to genomic instability and apoptotic cell death.[31] PARP1 also has a direct role in the HRR pathway at replication forks.[32] This dual role of PARP1 in DNA repair and the homologous recombinant repair pathway has been postulated as an important factor in the profound activity of PARP1/2 inhibitors in HRD cancer cells.[30]

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerization (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.[34]

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs).[25,27,33] Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Based on this rationale, we propose a single arm phase II study to evaluate the olaparib for the treatment of advanced biliary cancer expressing DNA repair mechanism defects.

1.4 Correlative Research

PARP inhibitors, such as olaparib act through synthetic lethality in cells with defects in homologous recombination (HR) DNA repair caused by molecular aberrations such as BRCA mutations and is approved for treatment in ovarian cancer and recently breast cancer, with promising clinical activity against other HR defective tumors including breast and prostate cancers. Nonetheless, in the majority of patients, resistance to PARP inhibition inevitably develops, leading to treatment failure. Additionally, a proportion of patients exhibit primary resistance to these drugs despite harboring genomic features of DNA repair deficiency.

Cancer genomes have mutational signatures associated with a variety of pathogenic processes including exposure to exogenous or endogenous mutagens, abnormal DNA editing, the incomplete fidelity of DNA polymerases and failure of DNA repair mechanisms. The latter include mutations and genomic scars associated with loss of wild type BRCA genes and an acquired homologous recombination deficiency (HRD). Clinical studies have shown extensive responses to agents that either increase the level of DNA damage (cisplatin) or interfere with repair of lesions (PARP inhibitors) in patients with pathogenic BRCA germ line variants. Significantly a wide variety of tumors including cancers of the gastrointestinal tract, have a HRD mutational signature even in the absence of pathogenic BRCA variants. The goal of this correlative study will be to determine the mutational profiles of biliary tract cancer in patients enrolled in the phase II study of olaparib. Of significant interest will be the identification of mutations in genes that mediate

DNA repair and HRD related mutational signatures that may correlate with clinical response.

To achieve our goal we will process diagnostic samples from each of 36 patients in the trial using our established flow cytometry and genomic methods. Briefly each sample will be screened by DNA content based flow cytometry to identify tumor and non-tumor populations in biopsies of interest. Once identified each population will be sorted and collected for downstream DNA processing and sequencing.

Cancer biopsies typically have variable levels of stromal and normal cell contamination. However in each case we will prepare tumor and patient matched normal DNA from flow sorted biopsies. Our use of purified flow sorted samples will provide high definition germ line and somatic mutational profiles including the discrimination of heterozygous and homozygous alleles for genes of interest. These will provide a unique data set to explore the associations of mutations and mutational signatures with clinical responses in advanced biliary tract cancer.

2.0 Goals

2.1 Primary

2.11 To determine the efficacy (Progression Free Survival (PFS) rate at 1st scan) of olaparib monotherapy in advanced biliary tract cancer (BTC) with mutations in DNA repair genes.

2.2 Secondary

2.21 To determine the overall survival of patients with advanced biliary tract cancer with mutations in DNA repair genes treated with olaparib.

2.22 To determine the progression free survival of patients with advanced biliary tract cancer with mutations in DNA repair genes treated with olaparib

2.23 To determine the objective response of patients with advanced biliary tract cancer with mutations in DNA repair genes treated with olaparib.

2.2 To assess the duration of response for patients with advanced biliary tract cancer with mutations in DNA repair genes treated with olaparib who experience an objective response.

2.25 To assess the frequency and severity of adverse events in advanced biliary tract cancer patients treated with olaparib.

2.3 Correlative Research

2.31 Determine the prevalence of mutations including those targeting DNA repair pathways.

2.32 Identify mutational signatures associated with pathogenic process in advanced biliary tract cancer samples

2.33 Correlate the presence of mutations and mutational signatures linked to mutations in DNA repair genes and homologous recombinant repair with clinical responses to olaparib

2.34 To evaluate putative biomarkers related to: (a) *de novo* sensitivity and (b) tumor evolution and resistance, to PARP inhibition from olaparib in BTC.

3.0 Patient Eligibility

NOTE: Waivers to eligibility criteria are not allowed per ACCRU policy

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histological or cytological documentation of metastatic adenocarcinoma of the biliary tract.

3.13 Patients with previously identified genetic aberrations that are associated with homologous recombinant repair pathway will be eligible [e.g. somatic mutations in *ATM, ATR, CHEK2, BRCA ½, RAD51, BRIP1, PALB2, PTEN, FANC, NBN, EMSY, MRE11, ARID1A] or* germline mutations in the above genes. CLIA-certified assays including commercial tests (Foundation Medicine, Caris, Tempus) will be allowed.

3.14 Measurable disease as defined in Section 11.0.

3.15 ECOG Performance Status (PS) 0 to 2. (Form is available on the ACCRU web site).

3.16 Life expectancy of ≥ 16 weeks per estimation of investigator.

3.17 The following laboratory values obtained ≤7 days prior to registration.

- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥75,000/mm^3
- Hemoglobin ≥9.0 g/dL with no blood transfusion in the past 28 days
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) and aspartate amino-transferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Serum creatinine ≤1.5 x ULN
- INR/aPTT ≤ 1.5 x ULN
  Exception: Patients who are therapeutically treated with anticoagulant agents will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care.
- Alkaline phosphatase limit ≤2.5 x ULN (≤5 x ULN for patients with liver involvement of their cancer)
- Creatinine clearance estimated of ≥51 mL/min using the Cockcroft-Gault equation.

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{\textbf{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\frac{\textbf{(140 - age)(weight in kg)(0.85)}}{\textbf{(72)(serum creatinine in mg/dL)}}$

3.18 Negative serum pregnancy test done ≤28 days prior to registration and confirmed prior to treatment on day 1, for women of childbearing potential, postmenopausal women or women of childbearing potential with evidence of non-childbearing status.

Postmenopausal is defined as:

- Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
- Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50
- Radiation-induced oophorectomy with last menses >1 year ago
- Chemotherapy-induced menopause with >1 year interval since last menses
- Surgical sterilization (bilateral oophorectomy or hysterectomy)

3.19a Provide informed written consent.

3.19b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19c Willing to provide blood and tissue for correlative purposes (see Sections 6.0 and 17.0).

3.19d HBsAg, anti-HBc and anti-HBs

3.19e Patients with chronic HBV receiving any systemic anticancer therapy should receive antiviral prophylactic therapy through and for minimum 12 months following anticancer therapy

3.19f Patients with past HBV undergoing other systemic anticancer therapies not clearly associated with a high risk of HBV reactivation should be monitored with HBsAg and alanine aminotransferase during cancer treatment (suggest every other cycle).

3.2 Exclusion Criteria

3.21 Platinum refractory disease which we define as:
1. Evidence disease progression on platinum based chemotherapy regimen or 2. Evidence of disease progression ≤6 months of completion of platinum based adjuvant chemotherapy regimen.

3.22 Patient has received prior systemic anti-cancer therapy, tumor embolization or radiotherapy ≤28 days prior to registration.

3.23 Major surgical procedure, open biopsy, or significant traumatic injury ≤28 days prior to registration.

NOTE: Patients must have recovered from any effects of any major surgery.

3.24 Congestive heart failure - New York Heart Association (NYHA) ≥ Class II.

3.25 Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg. unstable ischemia, uncontrolled symptomatic arrhythmia, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome. Cardiac arrhythmias requiring anti-arrhythmic therapy.

NOTE: Pacemaker, beta blockers or digoxin are permitted.

3.26 Uncontrolled hypertension – Grade 3 or higher per CTCAE v5.0 (despite optimal medical management).

3.27 History of or current pheochromocytoma.

3.28 Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism ≤6 months prior to registration.

3.29a Ongoing infection > grade 2 NCI-CTCAE v5.0.

3.29b Seizure disorder requiring medication.

3.29c Symptomatic metastatic brain or meningeal tumors unless the patient is > 6 months from definitive therapy, has a negative imaging study ≤ 28 days of registration and is clinically stable with respect to the tumor at the time of registration. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days prior to registration.

NOTE: The patient can receive a stable dose of corticosteroids before and during the study as long as these were started ≤ 28 days prior to registration.

3.29d History of organ allograft (including corneal transplant) or allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).

3.29e Evidence or history of bleeding diathesis or any hemorrhage or bleeding event >CTCAE v5.0 grade 3, ≤28 days prior to registration.

3.29f Non-healing wound, ulcer, or bone fracture.

3.29g Renal failure requiring hemo-or peritoneal dialysis.

3.29h Dehydration CTCAE v5.0 grade ≥2.

3.29i Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.

3.29j Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.

3.29k Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.

3.29l Persistent proteinuria of CTCAE v5.0 Grade 3 or higher (≥ 3.5 g/24 hrs).

3.29m Unable to swallow orally administered medications.

3.29n Any malabsorption condition and/or patients with gastrointestinal disorders likely to interfere with absorption of the study medication

3.29o Unresolved toxicity greater than CTCAE v5.0 Grade 2 attributed to any prior therapy/procedure excluding alopecia and oxaliplatin induced neurotoxicity ≤Grade 2.

3.29p Albumin levels <2.5 g/dl.

3.29q Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

NOTE: Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination (as described in Appendix V). This should be started from the time of registration and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (as described in Appendix V).

Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also

use a highly effective form of contraception (as described in Appendix V) if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

3.29r Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

3.29s Immunocompromised patients and patients known to be HIV serologically positive and currently receiving antiretroviral therapy.

NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

3.29t Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.29u Previous and/or intercurrent cancers. With the exception of: curatively-treated cancers with no recurrence in ≥ 5 years or early cancers treated with curative intent, including but not limited to cervical carcinoma in situ, superficial, noninvasive bladder cancer, basal cell carcinoma, squamous cell carcinoma in situ, , , ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma, or endoscopically resected gastrointestinal cancers limited in mucosal layer.

NOTE: All cancer treatments for cancers that were distinct in a primary site other than biliary tract cancer must be completed ≥3 years prior to registration.

3.29v Pleural effusion or ascites that causes respiratory compromise (≥CTCAE v5.0 Grade 2 dyspnea).

3.29w Previous enrollment in the present study

3.29x Prior exposure to any PARP inhibitor including olaparib.

3.29y Known hypersensitivity reaction to olaparib or any of the excipients of the product.

3.29z Myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

3.29aa 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).

NOTE: The required washout period prior to registration is 2 weeks.

3.29ab 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).

NOTE: The required washout period prior to registration is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

3.29ac Patient taking medications or herbal products including grapefruits, grapefruit hybrids, pomelos, star fruits, Seville oranges, pomegranates, or the juice from any of these. Note: Patients must discontinue the drug/product ≥ 7 days prior to registration.

3.29ad Patient taking medications with a known risk to prolong the QTc interval and/or cause Torsades de Pointes. Note: Patients must be discontinued ≥ 7 days of registration. Treating physicians may wish to replace the drug(s) that do not carry this risk with safe alternative(s).

3.29ae Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable outside of 28 days prior to treatment)

3.29af Involvement in the planning and/or conduct of the study

3.29ag Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements

4.0 Test Schedule

Tests and procedures	Active Monitoring Phase					
	≤7 days prior to registration	Cycle 1 (+/- 7 days) Week1 (Day 1)	Cycle 2 (+/- 7 days) Week 1 (Day 1)	After Cycle 2, Day 1 of every cycle until progression (+/- 7 days)	End of Treatment (at PD, withdrawal, or removal)	30 days after last dose of study drug (+/- 7 days)
History and exam, weight, ECOG PS[7], blood pressure	X	X[7]	X	X	X	X
Height	X					
Adverse event assessment	X	X	X	X	X	X
Hematology[5]: CBC/ differential, ANC, MCV, INR/aPTT	X	X	X	X	X	
Chemistry[5]: SGOT (AST), alk phos, T. bili, serum creatinine, calcium, glucose, Na, K, SGPT (ALT)	X	X	X	X	X	
Albumin, serum total protein[5]	X		X			
Urinalysis- White blood cells, red blood cells, protein, glucose, hyaline casts	X					
Tumor measurement (CT scan of chest, abdomen and pelvis) (MRI if CT is not feasible)	X[1]			X[1]	X[1,6]	
ECG[4]	X					
Serum pregnancy test	X[2]	X	X	X	X	
Mandatory Plasma blood collection (see Section 14.1)[R]		X		X[10]	X	
Mandatory archival tissue sample (see Section 17.0)[8, R]		X				
Optional tissue sample (see Section 17.0)[9,R]					X	
Patient Medication Diary (Appendix II)[3]		X	X	X	X	

1. CT scans preferred (MRI if CT is not feasible) of the chest, abdomen and pelvis. Use same imaging throughout the study. Tumor measurements at baseline (≤28 days prior to registration) and every 8 weeks until progression.
2. For women of childbearing potential only. Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment and at each subsequent visit during study treatment and at the 30 day follow up visit. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.
3. The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution during each scheduled visit.
4. Performed at screening and then as needed.
5. Hematology and chemistry tests to be done prior to each cycle. Activated partial thromboplastin time (APTT) will be performed at screening and if clinically indicated. International normalized ratio (INR) will be performed at screening and if clinically indicated. Each coagulation test result will be recorded in CRF. In case a patient shows an AST or ALT ≥3x ULN together with total bilirubin ≥2xULN please refer to Appendix 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law' for further instructions.
6. If patient goes off study during Cycle 1 and last CT scan was done >28 days prior, the CT scan must be done.
7. If baseline history, exam, weight, ECOG PS, and blood pressure were performed ≤3 days of Cycle 1 Day 1, they do <u>not</u> need to be repeated for Cycle 1 Day 1.
8. Archival tissue will be collected ≤28 after registration. Patients may initiate study treatment prior to the receipt of the archival tissue. See section 17.
9. Optional tissue collection at end of treatment.
10. At the time of radiographic assessment (Every 8 weeks).

R Research funded.

5.0 Stratification Factors OR Grouping Factor:

None

6.0 Registration Procedures

6.1 Site Procedures

6.11 Study staff will need to complete the required training prior to gaining access to the registration application. This is located on the ACCRU web page at [redacted] Refer to Study Resources → Applications. Near the bottom of the page there will be a link to the "Research Registration Application Training." After training is complete, study staff must complete the "Attestation of Training" and send to the ACCRU Registration Office at [redacted]

6.12 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using Florence.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using Florence. If the necessary documentation is not submitted in advance of attempting patient registration, the randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

6.2 Registration Procedures

6.21 To register a patient, access the ACCRU web page at [redacted] go to the Study Resources → Application section and click on "Registration" and enter the registration application. The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration application are available on the above web page under the Study Resources section→ Application section. Please refer to the "Research Registration Application Training" or Quick Reference Guide for instructions.

Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office at [redacted] If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to the Research Registration Application training on the ACCRU website under Study Resources → Applications.

□

6.22 Prior to accepting the registration, the registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.23 Correlative Research

Mandatory
A mandatory correlative research component is part of this study. The patient will be automatically registered onto this component (see Sections 3.0, 14.0 and 17.0).

Optional
An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Section 17.0).

- Patient has/has not given permission to give his/her tissue sample for research testing.

6.24 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.

6.25 Treatment cannot begin prior to registration and must begin ≤ 7 days after registration.

6.26 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.27 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.28 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention

Agent	Dose	Route	Frequency	ReRx
Olaparib	300mg (Starting dose)	PO	Twice Daily (28 day cycle)	Every 28 days

The planned dose of 300 mg taken twice a day will be made up of two (2) x 150 mg tablets, with 100 mg tablets used to manage dose reductions. The planned dose should be taken at the same times in the morning and evening of each day, approximately 12 hours apart with approximately 240 mL of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

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

7.2 Patients can be instructed in administration techniques and granted treatment independence with nursing staff approval.

7.3 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 28 days +/- 7 days during treatment.

8.0 Dosage Modification Based on Adverse Events

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

Once dose is reduced, escalation is not permitted.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Levels

Dose Level	**Drug Name**	**Drug Name**
1*	Olaparib	300mg taken orally twice daily
-1	Olaparib	250mg taken orally twice daily
-2	Olaparib	200mg taken orally twice daily

* Dose level 1 refers to the starting dose.

8.2 Dose Modifications

Management of hematological toxicity

Management of anemia

Hemoglobin	**Action to be taken**
Hgb < 10 *but* **≥ 8 g/dl** **(CTCAE Grade 2)**	First occurrence: Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) or interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dl. Subsequent occurrences: If Hb< 10 but ≥ 9 g/dl investigator judgement to continue olaparib with supportive treatment (eg transfusion) or dose interrupt (for max of 4 weeks) and upon recovery dose reduction may be considered (to 250 mg twice daily as a first step and to 200 mg twice daily as a second step). If Hb< 9 but ≥ 8 g/dl, dose interrupt (for max of 4weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered (to 250 mg twice daily as a first step and to 200 mg twice daily as a second step).
Hgb < 8 g/dl **(CTCAE Grade 3/4)**	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hgb ≥ 10 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat 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 CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence), refer to dedicated section "Management of prolonged hematological toxicities while on study treatment" for the management of these cases.

Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	*Study treatment dose adjustment*
CTCAE gr 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 gr 3-4	Dose interruption until recovered to CTCAE gr 1 for a maximum of 4 weeks, and dose reduction 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 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. Study treatment can be interrupted for CTCAE grade 1 /2 neutropenia or thrombocytopenia as per investigator's judgement. In case of CTCAE grade 3/4 neutropenia, leukopenia or thrombocytopenia, study treatment should be interrupted for a maximum of 4 weeks. Study treatment can be restarted at the same dose if an adverse event of neutropenia, leukopenia or thrombocytopenia has been recovered up to CTCAE grade 1 or less. Any subsequent interruptions will require study treatment dose reductions to 250 mg twice daily as a first step and to 200 mg twice daily as a second step.

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 anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse neutropenia (ANC < 1 x 109/L)
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia (Platelets < 50 x 109/L)

Weekly differential blood counts including reticulocytes and peripheral blood smear should be performed. Study treatment should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 4 weeks of dose interruption. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

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. Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety.

Management of non-hematological toxicity

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

permanently discontinue study treatment.

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

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

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. As per international guidance on antiemetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered e.g. dopamine receptor antagonist, antihistamines, 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 Principal Investigator.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF. Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

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

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

Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment. Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and nonclinical and asymptomatic laboratory abnormalities.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment

can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

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

Because the adverse effects 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.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality occurs, an interruption in study treatment dosing is recommended and a 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 Principal Investigator.

Renal impairment

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

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

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

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

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetic's may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO) Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3199-3212.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study

treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Concomitant Medications

The following medications below are to be avoided while on study:

Restricted concomitant medications

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

Restricted concomitant medications

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed):**
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • OATP1B1substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Administration of other anti-cancer agents	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

10.0 Adverse Event (AE) Reporting and Monitoring
The site principal investigator is responsible for reporting any/all adverse events to the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information.

NOTE: Please see Appendix III for specific AE reporting regarding the study drug olaparib.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Adverse events after the 30 day follow up period

For Pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

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

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

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

Olaparib adverse events of special interest

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

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

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established.

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 300 mg twice daily (tablet).

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

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.
For overdoses associated with a SAE, the standard reporting timelines apply. For other overdoses, reporting must occur within 30 days.

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
[redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 5.0.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.53 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).
NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.31 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.53). *

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
Gastrointestinal Disorders	Diarrhea	Any Grade
	Dyspepsia	
	Nausea	
	Vomiting	
	Colitis	Grades 1-3
	Pancreatitis	
General disorders and administrations site conditions	Fatigue (asthenia, lethargy, malaise	Any Grade
Hepatobiliary disorders	Cholecystitis	Grades 1-3
Infections and infestations	Lung Infection	Grades 1-3
	Sinusitis	
	Skin infection	
	Urinary tract infection	
Investigations	Alkaline phosphatase increased	Any Grade
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Lymphocyte count decreased	
	Weight loss	
Metabolism and nutrition disorders	Anorexia	Any Grade
	Dehydration	
	Hyperkalemia	
	Hypocalcemia	

	Hypomagnesemia	
	Hyponatremia	
Musculoskeletal and connective tissue disorders	Arthralgia	Any Grade
	Back pain	
	Musculoskeletal and connective tissue disorder – Other (muscle spasms)	
Skin and subcutaneous tissue disorders	Alopecia	Any Grade
	Rash acneiform	
	Rash maculo-papular	
	Palmar-plantar erythrodysesthesia syndrome	

These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

*Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study) site over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event

*An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

10.331 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

    - Death attributable to a CTCAE term.

    - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

    - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Death due to progressive disease should be reported as **Grade 5 "Disease progression"** under the system organ class (SOC) General Disorders and Administration Site Conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.332 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

    - Myelodysplastic syndrome (MDS)

    - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.333 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.334 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected. *In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.*

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study drug

- Pregnancies in the partner of male subjects

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

Maternal exposure
If a patient becomes pregnant during the course of the study, olaparib should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) occurring from the date of the first dose of study medication until 1 month after the last dose of study medication should be followed up and documented even if the patient was discontinued from the study.

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Paternal exposure

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

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) occurring from the date of the first dose until 3 months after the last dose should, if possible, be followed up and documented.

10.4 Expedited Adverse Event Reporting Requirements Studies using Commercial Agent(s) ONLY:

10.41 Expedited Reporting via the **MedWatch 3500A Form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Commercial Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour; 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Special Instructions:

- Follow site-specific reporting guidelines.
- Expedited reports must be submitted to the FDA vis MedWatch 3500A Form found: [redacted]

[redacted]

- Instructions for completing the MedWatch 3500A: [redacted]
- Submit copies along with the US ESR SAE Report Coversheet found on the ACCRU Website to the ACCRU SAE Coordinator via email at [redacted]
- The ACCRU SAE Coordinator will forward to the funding sponsor via email at [redacted]
- The ACCRU SAE Coordinator will forward to ACCRU IND Coordinator [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.
If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and adverse events are to be graded at each evaluation using CTCAE v5.0 grading. If CTCAE v5.0 grading is not used, note the grading scale used in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Gastrointestinal disorders	Diarrhea	# stools per day	X
	Nausea	X	X
	Vomiting	X	X
General Disorders and administration site conditions	Fatigue	X	X
Skin and Subcutaneous Tissue Disorders	Palmar-plantar erythrodysesthesia syndrome	X	X
	Rash maculo-papular	X	X
Vascular disorders	Hypertension	X	X

10.53 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU)
Submit the following AEs not specified in Section 10.5

10.531 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.532 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.533 Grade 5 AEs (Deaths)

10.5331 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure requires the submission of an Expedited Adverse Event report (see Section 10.4).

10.5332 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned with an Expedited Adverse Event report (see Section 10.4).

11.0 Treatment Evaluation Using RECIST Guideline

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measurable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (Eisenhauer et al., 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 8 weeks.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions representative of all involved organs, should be identified as “Target Lesions” and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm.

- Partial Response (PR):At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431
** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

For Patients with Non-Measurable Disease Only:

Non-Target Lesions & Non-Target Lymph Nodes	**New Sites of Disease**	**Overall Objective Status**
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not All Evaluated*	No	Not Evaluated (NE)
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*See Section 11.431

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Anatomic location done: Yes vs. no.

12.11 If yes, (intrahepatic, extrahepatic or gallbladder cancer)

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

- If the patient never received treatment, on-study material must be submitted.

13.2 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are no safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol, and all data submission should continue per protocol. If the patient does not continue with treatment, the patient will go Off Treatment and be followed in Survival Follow-up

13.3 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.4 Patients will continue treatment until progression or a maximum of 36 cycles, unacceptable adverse events, or patient refusal. Treatment will then be discontinued and the patient will go to event monitoring and be followed per Section 18.0.

13.5 Patients who are CR, PR, or SD will continue treatment per protocol or a maximum of 36 cycles.

13.6 Patients who develop PD while receiving therapy will go to the event-monitoring phase and will be followed for survival (i.e. event-monitoring phase) every 3 months (±7 days) for 3 years after registration (per Section 18.0).

13.7 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase and be followed for survival and progression (i.e. event monitoring phase) every 3 months (±7 days) for 3 years after registration (per Section 18.0).

13.8 Event Monitoring is not part of the Active Monitoring phase of a study and is defined as the time period when the participant is no longer following the protocol test schedule. During Event Monitoring, the data collection schedule is dictated by the protocol but the visit schedule is determined by clinical practice at each participating site. During the Event Monitoring Phase of the study, the participant is being monitored for key study events such as progression, new primaries, and death. Event monitoring should occur every 3 months (± 7 days) until death or a maximum of 3 years following Registration. Phone or virtual visits are permitted during Event Monitoring.

13.9 The patient will be withdrawn from treatment if there are bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML). The patient will go to the event-monitoring phase per Section 13.7.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Indicate if specimen is mandatory or optional	**Collection tube description and/or additive (color of tube top)**	**Volume to collect per tube (number of tubes to be collected)**	**Blood product being processed and submitted by participating site**	**Baseline[1, 5]**	**Restaging[2]**	**End of Treatment[3]**	**Additional processing required at site after blood draw?**	**Storage /shipping conditions[4]**
Mandatory	Streck	10 ml (2)	Whole blood into Platelet Poor Plasma	X	X	X	No	Ambient/ Room Temperature

1. May occur prior to treatment on Cycle 1 Day 1.
2. At the time of radiographic assessment (Every 8 weeks).
3. Discontinue of study treatment.
4. After all samples have been processed according to kit instructions, ship all specimens According to shipping instructions (see Section 14.3 for detailed shipping instructions.)
5. Blood draws should not be collected and submitted until after the patient is registered onto the study.

14.2 Kits are required for this study.

14.21 Each kit will contain supplies and instructions for collecting, processing, and shipping specimens.

14.22 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Supply form. A small but sufficient supply of the specimen collection kits should be ordered prior to patient entry. Unused/expired kits should be disposed of per institution policy. Do not send unused kits back. **Supply Order Forms must be filled in completely and legibly for quick processing.**

14.23 Kits will be sent via FedEx Ground at no cost to the participating institutions. **Allow up to two weeks to receive the kits.** Kits will arrive inside the shipping boxes.

14.24 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx account number or alternate billing number for express service. **ACCRU will not cover the cost for rush delivery of kits.**

14.3 Shipping and Handling

14.31 Verify ALL sections of the Blood Specimen Requisition Form (Provided in kit) and specimen collection labels are completed and filled in correctly.

14.32 Specimens must be shipped the same day they are drawn.

14.33 Ship tubes at room temperature. See kit instructions for specific details.

14.34 Ship specimens via Priority Overnight service, Monday-Thursday, to Mayo Biobank according to kit instructions. Do not send samples on weekends or just prior to federal holidays. If a patient can only be seen on Fridays, email the Biospecimen Manager (found on resource page located on the ACCRU website) with the sample information and FedEx tracking number.

Biobank address:

[redacted]

14.35 The kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an air bill. Shipping costs will be covered by ACCRU if the shipping box provided with the BAP kit is used for shipping specimens to Mayo Biobank.

14.36 Mayo Biobank will receive the samples and forward specimens to [redacted] laboratory.

14.4 Study Methodology and Storage Information

14.41 Blood/blood product samples will be collected for the following research

14.411 [redacted] laboratory will initially analyze a portion of the DNA for the presence of genes associated with homologous recombinant deficiency or novel genomic alterations, using standard laboratory protocols. Remaining DNA will be stored frozen at -70ºC by Mayo Biobank, according to patient consent information (see Section 6.0) until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.)

14.412 A portion of the plasma will initially be analyzed for the presence of tumor genomic biomarkers in [redacted] laboratory using standard laboratory protocols. According to patient consent information (see Section 6.0), remaining plasma will be stored frozen at -70ºC by Mayo Biobank, until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.)

14.413 As part of ongoing ACCRU research, we will collect plasma for future research studies, according to patient consent information (see Section 6.0), on molecular determinants of efficacy and tolerability. Samples will be stored frozen at -70ºC by Mayo Biobank until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval.

14.4 Return of Genetic Test Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

IND exempt

- Refer to package insert for complete, up-to-date information.

15.1 **Olaparib (Lynparza™, AZD2281):**

15.11 **Background:** Olaparib is a potent inhibitor of polyadenosine 5’diphosphoribose

polymerase (PARP) developed as a monotherapy as well as for combination with chemotherapy, ionizing radiation and other anti-cancer agents including novel agents and immunotherapy.

15.12 **Formulation**: Olaparib is presented for oral administration as a film-coated tablet containing 100 mg or 150 mg of drug substance. The 100 mg strength is also available film-coated tablet. The tablet cores comprise: olaparib, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. The composition of the tablet film coating is: hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black. Olaparib tablets are supplied in high-density polyethylene (HDPE) bottles containing desiccant. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence. Olaparib is presented for oral administration as a white, hard shell, size 0 capsule containing 50 mg drug substance. The fill for the 50 mg olaparib capsules comprises olaparib and lauroyl macrogolglycerides (lauroyl polyoxylglycerides). This is filled into capsule shells, which are composed of hypromellose, gellan gum, potassium acetate and titanium dioxide. Capsules may be printed; the ink used for printing comprises shellac and iron oxide black. Olaparib capsules are supplied in HDPE bottles. Bottles are secured with a child-resistant and tamper-evident closure. Each container will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.

15.13 **Preparation and storage**: The product should be stored in the pack provided and used according to the instructions on the label.

15.14 **Administration:** Administer with or without food. Swallow capsules whole; do not chew, dissolve, or open capsule. Swallow tablets whole; do not chew, crush, dissolve, or divide tablet. Given the different drug delivery technologies in the capsule and tablet, the formulations cannot be considered to be bioequivalent. Do not substitute the 50 mg capsules for the 100 mg or 150 mg tablets on a mg-per-mg basis. Do not consume grapefruit or grapefruit juice while taking olaparib.

15.15 **Pharmacokinetic information**:
Absorption: Rapid; delayed with a high-fat meal (extent of absorption not significantly altered).
Time to peak: Capsule: 1-3 hours; tablet: 1.5 hours
Bioavailability: Tablet formulation has higher bioavailability than the capsule formulation
Distribution: Capsule: 167 liters; tablet: 158 liters
Metabolism: Primarily hepatic via CYP3A4; the majority of metabolism is through oxidation with some metabolites undergoing subsequent glucuronide or sulfate conjugation
Half-life elimination: Capsule: 11.9 hours; tablet: 14.9 hours
Protein binding: ~82%
Excretion: Urine (44%, mostly metabolites); feces (42%, mostly metabolites)

15.16 **Potential Drug Interactions**:
CYP3A4/5 are the isozymes predominantly responsible for the metabolic

clearance of olaparib. Clinical studies conducted with a tablet formulation to evaluate the impact of known CYP3A inhibitors and inducers have shown that co-administration of a potent CYP3A inhibitor, itraconazole, increased olaparib Cmax by 142% and increased mean AUC by 270% and that co-administration of a potent CYP inducer, rifampicin, decreased Cmax by 71% and mean AUC by 87%. Moderate inhibitors and inducers of CYP3A are also predicted to significantly alter the exposure of olaparib. It is therefore recommended that known strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib.

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

Caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (eg, irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP2B6 being most likely to be induced to a clinically relevant extent. It cannot be excluded that olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes.

Olaparib may modulate the exposure to substrates of OATP1B1 (eg, bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (eg, metformin), OCT2 (eg, serum creatinine), OAT3 (furosemide, methotrexate), MATE1 and MATE2K (metformin). In particular, caution should be exercised if olaparib is administered in combination with any statin.

Co-administration of topotecan reduced steady state exposure to olaparib by approximately 20%.

15.17 **Known potential toxicities**:

Very Common potential toxicities (> 10%):

Cardiovascular: Peripheral edema, edema
Central nervous system: Fatigue, headache, dizziness
Dermatologic: Dermatitis, skin rash
Endocrine & metabolic: Hypomagnesemia
Gastrointestinal: Nausea, abdominal pain, vomiting, diarrhea), dysgeusia, dyspepsia, constipation, decreased appetite, stomatitis, upper abdominal pain
Genitourinary: Urinary tract infection
Hematologic & oncologic: Increased MCV, decreased absolute lymphocyte count, anemia, decreased platelet count, neutropenia, leukopenia
Infection: Influenza
Neuromuscular & skeletal: Weakness, musculoskeletal pain, arthralgia, myalgia,

back pain
Renal: Increased serum creatinine
Respiratory: Nasopharyngitis, respiratory tract infection, rhinitis, sinusitis, cough, dyspnea
Miscellaneous: Fever

Common potential toxicities, 1% to 10%:
Cardiovascular: Hypertension, venous thrombosis (embolism)
Central nervous system: Anxiety, depression, insomnia, peripheral neuropathy
Dermatologic: Pruritus, xeroderma (including eczema)
Endocrine & metabolic: Hot flash, hyperglycemia
Genitourinary: Dysuria, urinary incontinence, vulvovaginal disease
Hematologic & oncologic: Myelodysplastic syndrome

Uncommon potential toxicities, <1%: Hypersensitivity reaction, pneumonitis

15.18 **Drug procurement:** AstraZeneca will supply the drug to Clinical Research Services, a division of Rx Crossroads by McKesson. Each participating ACCRU treating location will order the drug from Clinical Research Services. Submit the Drug Order Request Form (found on the ACCRU web site) to:

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of olaparib and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19a Temperature excursions that occur at the site should be reported by the site by calling AZ medical information at [redacted] to get temperature data in order to determine fit for use.

Any shipment deviations (those not occurring at the site) should be reported to Clinical Research Services via email to:
[redacted]

15.19b **Nursing Guidelines:**

15.19b1 Olaparib may be administered with or without food. Patients must be instructed to swallow pills whole.

15.19b2 Grapefruit or grapefruit juice is prohibited while taking olaparib.

15.19b3 Assess patients medication list including OTC and herbal products while patients are taking olaparib as there are many drug to drug interactions.

15.19b4 Instruct patients to report any edema. Rarely patients may experience

venous thrombosis.

15.19b5 Patients may experience headache, dizziness while on olaparib. Instruct patients to use caution when doing tasks that require attention, until they can ascertain their tolerability to olaparib.

15.19b6 Gastrointestinal side effects are common, including nausea, vomiting, diarrhea, etc. Treat symptomatically and monitor for effectiveness.

15.19b7 Monitor CBC w/diff as cytopenias are common. Instruct patients to report any unusual bruising or bleeding and/or signs symptoms of infection to the study team.

15.19b8 Monitor renal function and assess for any urinary symptoms. Patients may experience urinary tract infection and/or increased creatinine.

15.19b9 Patients may experience rhinitis, respiratory tract infection, cough, etc. Treat symptomatically and monitor for effectiveness of intervention.

16.0 Statistical Considerations and Methodology

16.1 Overview

This single arm phase II study will assess the efficacy of Olaparib monotherapy in advanced biliary tract cancer (BTC) patients (including gallbladder, intra- and extrahepatic cholangiocarcinoma) that have received at least one line of prior chemotherapy (or have refused chemotherapy if eligible) with evidence of tumor somatic variants associated with homologous recombinant repair, or homologous recombinant deficient (HRD), or HRD-positive tumors. The primary endpoint is Progression-Free Survival (PFS) at the first scan (approximately 8 weeks). Treatment will be administered daily, where patients will receive 300mg by mouth twice daily. Each cycle will be 28 days. Patients will have response assessment by CT scan at 8-week intervals. Following each CT scan, only patients with disease control (defined as complete response, partial response, or stable disease) will continue on treatment until disease progression, intolerance, withdrawal from protocol therapy, or intercurrent illness.

16.2 Statistical Design

A Simon's two stage design will be used. The largest success (defined as progression-free and alive at 2 months) proportion where the proposed treatment regimen would be considered ineffective is 50%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 70%. The following two-stage design uses 14 or 30 evaluable patients to test the null hypothesis that the true success proportion in this given patient population is at most 50%.

16.21 Primary Endpoint

The primary endpoint for this trial is Progression-Free Survival at the first scan (approximately 8 weeks). A patient is defined as a success if the patient is progression free and alive at the first disease evaluation scan. Disease status will be assessed using RECIST v. 1.1 criteria. Evaluable patients are those who are

eligible, consented, and received any protocol treatment. The PFS rate will be calculated as the proportion of evaluable patients who are progression free and alive at the first disease assessment scan. The final PFS rate point estimate and corresponding 95% confidence interval will be reported according to the method of Clopper-Pearson.

16.211 STAGE 1:
Enter 14 patients into the study. If 7 or fewer successes are observed in the first 14 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 8, we will proceed to Stage 2.

16.212 STAGE 2:
Enter an additional 16 patients into the study. If 18 or fewer successes are observed in the first 30 evaluable patients, we will consider this regimen ineffective in this patient population. If 19 or more successes are observed in the first 30 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

16.213 NOTE:
We will not suspend accrual between stages to allow the first 14 patients to become evaluable, unless undue toxicity is observed.

16.22 Power and Sample Size

This two-stage study design outlined in 16.21 assumes the number of successes is binomially distributed, the null success proportion is 0.5, and the alternative success proportion is 0.70. Given these, the exact type 1 error rate (alpha) is 0.091, and the exact power is 80.6% when the true PFS rate is 70%.

A minimum of 14 and a maximum of 30 evaluable patients will be accrued onto this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 6 patients to account for ineligibility, cancellation, or other reasons. Maximum projected accrual is therefore 36 patients.

Operating characteristics were generated using R software.

If the true success proportion is:	0.5	0.55	0.6	.65	0.7
then the probability of stopping at stage 1 is:	0.604	0.457	0.313	0.184	0.095
then the probability of declaring that the regimen warrants further studies is:	0.091	0.210	0.398	0.613	0.806

16.24 Accrual Time and Study Duration

The anticipated accrual rate is approximately 2-3 patients per month. Therefore, the accrual period for the first stage of this phase II study is expected to be approximately 6 months. If patients are accrued beyond the first stage, the total accrual period is expected to be approximately 15 months. The final analysis can begin approximately 17 months after the trial begins; as soon as all patients have progressed, died, or received their first disease evaluation scan.

16.25 Over Accrual:

If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision-making process. However, they will be included in final point estimates and confidence intervals as though they were accrued in the final stage.

16.26 Other Considerations

Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Secondary Endpoints

The following objectives will be evaluated: overall survival, progression-free survival, objective response, duration of response, and adverse events.

16.31 Overall Survival (OS)

Overall survival is defined as the time from study entry to death from any cause. Patients who are still alive at the time of analysis will be censored at the time of their last study assessment (if still actively on study) ot at the date patient was last known to be alive (if in survival follow-up). OS will be estimated using the Kaplan-Meier method. The median OS and corresponding 95% confidence interval (by Brookmeyer and Crowley) will be reported.

16.32 Progression-Free Survival (PFS)

Progression-free survival is defined as the time from study registration to disease progression, as defined by RECIST 1.1, or until death, whichever occurs first. Patients who do not experience disease progression or death while on protocol will be censored at their last disease assessment date. PFS will be estimated using the Kaplan-Meier method. Median PFS and corresponding 95% CIs (by Brookmeyer and Crowley) will be reported.

16.33 Objective Response

Objective Response (unconfirmed) is defined as achieving a complete or partial response while on treatment. The objective response rate (ORR) will be calculated as the proportion of evaluable patients who achieve objective response. Disease status will be assessed using RECISTSv1.1 criteria. Evaluable patients are defined as those who are eligible, consented, and received any protocol treatment. Confidence intervals for the true success proportion will be calculated according to the approach of Clopper and Pearson.

16.34 Duration of Response

Duration of response (DoR) is defined for all evaluable patients who have achieved an objective response as the date at which the patient's earliest best objective status is first noted to be either a CR or PR to the earliest date progression is documented, or death if no prior evidence of disease progression. The distribution of DoR will be estimated using the method of Kaplan-Meier. The median DoR and corresponding 95% confidence interval will be reported.

16.354 Adverse Events

All patients who have initiated treatment will be considered evaluable for adverse event analyses. Adverse events by patient will be summarized by frequencies and severity using CTCAE version 5.0. The proportion of patients who experience at least one grade 3+ adverse event (regardless of attribution) will be reported.

16.4 Correlative Research

Genomic analyses will be performed on mandatory blood samples collected from patients at the start of therapy, every 8 weeks, and at progression. An optional biopsy will be performed at the time of disease progression. Additionally, all patients who consent to the study also provide consent for the collection of previously collected paraffin embedded tissue. Analysis methods may include RNASeq, flow sorting enabled whole exome sequencing, and whole methylome analysis at multiple timepoints. These analyses would be performed in the laboratory of [redacted] at Mayo Clinic Arizona (see Section 14.0).

Specific goals of the correlative research include the following:

16.41 To determine the prevalence of mutations including those targeting DNA repair pathways.

16.42 To identify mutational signatures associated with pathogenic process in advanced biliary tract cancer samples.

16.43 To correlate the presence of mutations and mutational signatures linked to mutations in DNA repair/HRR with clinical responses.

16.44 To evaluate putative biomarkers related to: (a) *de novo* sensitivity and (b) tumor evolution and resistance, to PARP inhibition in BTC.

16.5 Data & Safety Monitoring

16.51 Review

The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center

(MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules

Olaparib is an approved therapy in other diseases, the safety profile is well established, and the therapy is considered safe.[27, 33-35]

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered to be clinically relevant and at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

- If 2 or more patients in the first 20 treated patients (or 10% of all patients after 20 are accrued) experience a grade 3+ non-hematologic adverse event.

We note that we will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.55 CT.gov Reporting

Expected durations and timelines for certain events (e.g. accrual) and endpoints for CT.gov reporting purposes can be found in sections 16.24 and 16.21 respectively.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	**Mandatory**	**When to submit**	**Reason for submission (background/methodology section)**
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E	Mandatory	≤**28** days after registration	Correlative studies (Section 17.5)

Fresh Frozen Tumor Tissue (2-3) cores	Optional	EOT	Correlative studies (Section 17.5)
Formalin-Fixed paraffin embedded (FFPE) tissue blocks with corresponding H&E	Optional	EOT[1]	Correlative Studies (Section 17.5)

[1] Submit if fresh frozen is not obtained.

Archival tissue will be collected for correlative studies and to confirm HRD status. Patients may initiate study treatment prior to the receipt of the archival tissue. Additional tumor and unaffected liver tissue may be collected at the time of standard of care biopsy for diagnostic confirmation if a clear histologic diagnosis is unable to be made with archival tissue. At end of treatment, if a biopsy for routine clinical molecular profiling (using commercial assays such as Foundation One or Caris) is done, again, additional tumor and liver tissue may be obtained. For both time points (at time of standard of care diagnostic confirmation and at end of treatment when performing routine clinical molecular profiling), additional preferably fresh frozen 2-3 cores of tumor tissue using an 18 gauge needle should be collected. Tissue will be flash frozen and stored in a -80 degree freezer or shipped on dry ice to the [redacted] laboratory. If fresh frozen tissue is not available, archival tissue may be used. Collection of additional tissue at time of standard of care biopsies at screening and end of treatment likewise is optional.

17.2 Paraffin Embedded Tissue Blocks/Slides

17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) (from either primary or metastatic site). **A corresponding H&E slide for each submitted block must be provided. The H&E slide for each block should be reviewed by the institution's pathologist** to assess tissue quality prior to submission.

17.22 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, If not available in this format, up to 3 unstained, standard 50 micron scrolls/curls can be sent. **Label the tubes with ACCRU patient ID number, accession number, and order of sections (4-5 microns).** H&E stain the first and last slide (i.e., slides labeled 1, 3, etc.). The H&E slides should be reviewed by the institution's pathologist to assess tissue quality prior to submission. **Do not bake or place covers slips on the slides**.

17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks with corresponding H&E slide (OR 3 unstained slides with corresponding H&E(s)).
- Specimen Submission: Tissue form
- Surgical Pathology Report
- Operative Report *(optional)*
- **Note: Please include the ACCRU patient ID number on all materials listed above.**

17.24 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials. During warm weather months, paraffin blocks should be shipped using a refrigerant pack to avoid heat that may melt paraffin and damage blocks.

17.25 FFPE tissue specimens must be shipped ≤**28** days after registration.

17.26 Verify that the appropriate sections of the Specimen Submission: Tissue form are completed and filled in correctly. Enter information from the Specimen Submission: Tissue form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).

17.27 Ship all block/slide tissue specimens and accompanying materials to the Mayo Biobank:

[redacted]

17.28 The block and appropriate paperwork will be returned to the Mayo Clinic, [redacted]

17.29 When an appropriate request is submitted, the Mayo Biobank will forward the block/slides to [redacted] Mayo Clinic Arizona, for processing as outlined in Section 17.5.

17.3 Frozen Tumor tissue:

Biopsies (25-50 mgs) will be thawed then minced in the presence of NST buffer and DAPI according to published protocols [36,37]. Nuclei from each sample will be disaggregated then filtered through a 40μm mesh prior to flow sorting with an Influx cytometer (Becton-Dickinson, San Jose, CA) with ultraviolet excitation and DAPI emission collected at >450 nm. DNA content and cell cycle will be analyzed using the software program MultiCycle (Phoenix Flow Systems, San Diego, CA).

17.4 Study Methodology and Storage Information

17.41 Submitted tissue samples will be analyzed as follows:

We will focus on whole exome methods for these FFPE samples. As part of this study we will screen each sorted sample with our established quality control (QC) metrics. These will include tumor content, cellular debris, DNA yield, and fragment sizes prior to library preparation. Based on our experience with metastatic biopsy FFPE samples from clinical trials we anticipate that 10-12 cases

will be suitable for our whole exome analyses.

17.42 Next Generation Sequencing:

17.421 DNA templates

The DNA from each sorted tumor and a patient matched normal sample will be extracted with our standard protocols. Normal DNA will be extracted from either blood samples or the non-tumor fraction from sorted tissues. All DNAs will be assessed with our QC assays and metrics.

17.422 Whole genome sequencing of sorted frozen samples

A 1ug aliquot of high molecular weight DNA from each tumor and normal sample of interest will be used for all whole genome sequencing. The quantity and quality of each sample will be assessed by standard QC metrics using a QuBit fluorometer prior to shipping to the Mayo Genome Facility (MGF) in Rochester.

17.423 Whole exome sequencing of sorted FFPE samples

For FFPE samples we will use ThruPLEX® DNA-seq Kit to prepare paired-end libraries for each sorted tumor population and matching normal sample of interest. We will use a minimum input of 10ng for all library preparations. Aliquots of each library will be QC'ed on a BioAnalyzer prior to shipment to the MGF. Subsequently, whole exon capture will be carried out with Agilent's SureSelect Human All Exon 71 MB v6 kit. Briefly 500 ng of the prepped library is incubated with whole exon biotinylated RNA capture baits supplied in the kit for 24 hours at 65 °C. The captured DNA:RNA hybrids are recovered using Dynabeads MyOne Streptavidin T1 (Dynal). The DNA is eluted from the beads and desalted using purified using Ampure XP beads (Agencourt).The purified capture products were then amplified using the SureSelect Post-Capture Indexing forward and Index PCR reverse primers (Agilent) for 12 cycles. Libraries were loaded onto paired end flow cells at concentrations of 4-5 pM to generate cluster densities of 600,000-800,000/mm^2 using the Illumina cBot and HiSeq Paired end cluster kit version 3.The flow cells are sequenced as 101 X 2 paired end reads on an Illumina HiSeq 2500 or 4000 using TruSeq SBS sequencing kit version 3 and HiSeq data collection version 1.4.8 software. Base-calling was performed using Illumina's RTA version 1.12.4.2.

17.43 Data Analysis:

17.431 Mutation calling

All secondary analyses will be done through the Mayo Clinic Bioinformatics Core (BIC). This will include filtering observed variants based on a series of criteria including NextProt Feature Strength, Maximum Population Allele Frequency, and inclusion in the Catalogue of Somatic Mutations in Cancer (COSMIC) database [38]. The goal will be to prioritize those variants that likely disrupt protein function, identify mutations targeting known cancer related DNA repair genes and pathways, and filter out common polymorphisms reported in dbSNP and

other population based studies.

17.432 Mutational signature

We will work with Mayo Clinic bioinformaticians to extract mutational signatures from the next generation sequencing (NGS) data from each sample of interest. Of significant interest will be the presence of a HRD associated signature (Signature 3) that associates strongly with elevated numbers of large (longer than 3bp) insertions and deletions with overlapping microhomology at breakpoint junctions.

Instructions for shipment of samples to the analysis laboratory and shipping supplies will be provided by the Coordinating Center. All flow sorting of tissue samples, DNA extractions, and FFPE library preparations will be done in the [redacted] laboratory on the MCA Scottsdale campus.

17.44 At the completion of the study, any unused/remaining material will be stored in in Johnson Research Building 3-308 at Mayo Clinic Arizona for future research according to the patient consent permission (see Section 6.5). Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

17.45 Banking of tumor tissue, according to the patient consent permission (see Section 6.5), is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for ACCRU melanoma studies).

17.46 The institutional pathologist will be notified by the Biospecimen Manager if the block may be depleted.

17.47 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.5 Return of Genetic Testing Research Results

No genetic specimens will be collected from tissue biospecimens for this study. If future genetic testing is being requested for stored tissue, patient reconsent is required.

18.0 Records and Data Collection Procedures

All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at [redacted] All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted]

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
On-Study	
On-Study: Prior Systemic Therapy[1]	
Adverse Event: Baseline	
RECIST Measurements: Baseline	
Laboratory Tests & Results: Baseline	
Supporting Documentation: Baseline[2]	
Concomitant Medications	
Specimen Submission: Blood (Baseline) (see Section 14.0)	
Patient Status: Baseline	
OP and Path Reports (see Section 17.0)[2]	
Specimen Submission: Tissue (Baseline) (see Section 17.0)	< 28 days after registration
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
ACCRU Deviation Form[1]	Submit only if applicable during ***all*** **phases** of the study (initial, active and observation)

1. Submit only if applicable.
2. Upload via the Supporting Documentation: Baseline form. This is in addition to the pathology material requirements for tissue submission (Section 17.0). Tumor molecular profiling report demonstrating genetic aberrations that are associated with homologous recombinant repair pathway for eligibility.

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Treatment (Intervention)	X	X
Treatment (Intervention): Dose Modifications, Omissions and Delays[1]	X	
Adverse Events: Solicited	X	X
Adverse Events: Other[1]	X	X
RECIST Measurements[2]	X	X
Supporting Documentation[2]	X	X
Concomitant Medications	X	
Specimen Submission: Blood (see Section 14.0)[1]		
Specimen Submission: Tissue (see Section		

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
17.0)[1]		
Patient Status: Treatment (Intervention)	X	X
Notice of New Primary[1]	X	X
Consent Withdrawal (choose appropriate form)[1] • Consent Withdrawal: Specimen Only • Consent Withdrawal: All Follow-Up	X	X
Off Treatment		X
ACCRU Deviation[1]	X	X

1. Submit only if applicable.
2. Upload documentation of response or progression on the Supporting Documentation form.
3. Patients are eligible to be confirmed lost to follow-up after 2 years of unsuccessful contact with the patient.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q. 3 mos.	Death	New Primary
Patient Status: Survival and Disease Status Follow-Up/Event Monitoring	X[2]	X[2]	X	X	At each occurrence
Adverse Events: Late[3]					X
Supporting Documentation[3]					
Notice of New Primary[3]					X
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Specimen Only • Consent Withdrawal: All Follow-Up					X
Lost to Follow-Up[3]					
ACCRU Deviation Form[3]	X[3]	X[3]	X[3]	X[3]	

1. If a patient is still alive 3 years after registration, no further follow-up is required.
2. Upload a copy of documentation of response or progression in RAVE on the Supporting Documentation Form.
3. Submit only if applicable.

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Appendix I: ACCRU-ICRN-1702 Patient Drug Diary

Name:	Patient ID Number:
Cycle:	
You will take __tabs in the MORNING and __ tabs in the EVENING.	

ORAL MEDICATION DIARY
Patient Instructions

- Please bring your Medication Diary and any empty or unused medication container(s) with you to every appointment
- Please use an ink pen when completing the Medication Diary as these will be retained in our research record.
- Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should stop taking your medication or continue it.
- To correct an error or mistake, please make a single line through that entry and write your initials and date next to the error or mistake.
- Please record each dose as soon as you take it and fill in the date as directed.
- Please indicate on the calendar below every day you take your study medications by placing the time dose was taken on the line under the date.
- If you miss a dose, place a check "0" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- Take tablets by mouth daily as prescribed on days 1-28 of each cycle.
- If you accidentally take more than you are instructed to, contact your doctor or the emergency room immediately.
- If you miss a dose, do not make up the dose or double up on the next dose.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date:							
Time of Morning Dose	AM	AM	AM	AM	AM	AM	AM
Time of Evening Dose	PM	PM	PM	PM	PM	PM	PM
	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Date:							
Time of Morning Dose	AM	AM	AM	AM	AM	AM	AM
Time of Evening Dose	PM	PM	PM	PM	PM	PM	PM
	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Date:							
Time of Morning Dose	AM	AM	AM	AM	AM	AM	AM
Time of Evening Dose	PM	PM	PM	PM	PM	PM	PM
	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Date:							
Time of Morning Dose	AM	AM	AM	AM	AM	AM	AM
Time of Evening Dose	PM	PM	PM	PM	PM	PM	PM

APPENDIX II: OLAPARIB SAFETY DATA EXCHANGE REQUIREMENTS

1. STUDY IDENTIFICATION

Sponsor/Sponsor-Investigator:	<< insert name of Sponsor/Sponsor-Investigator>>
Sponsor/Sponsor-Investigator <<Study Title>> << Study No.>>	<< Insert Study Title and/or Study No. and/or Project title>>
AstraZeneca reference <<study/project>> number(s)	<<Insert AstraZeneca ESR tracking number and D-code>>
Sponsor/Sponsor-Investigator Study/project acronym:	<<Insert Study or project acronym>>

See summary table at the end of this document for further details

2. Before the study starts

Sponsor/Sponsor-Investigator will provide AstraZeneca with:

- A copy of the format of the (S)AE report form and cover letter, for reporting from investigator to sponsor. SAE form and/or cover letter must include the AstraZeneca Reference number(s).

An example of the format by which SAEs (including SUSARS) and AESIs will be reported from sponsor to AstraZeneca. This may be the same form used for reporting SAEs as above. This must include the AstraZeneca ESR Tracking number and contact details for reporting to AstraZeneca (e-mail address or fax number e.g.

- The format by which site and patient ID will be presented in safety data so that they can be entered in a consistent way on the AstraZeneca safety database.

  Please provide here: __ __ __ __ __ __ __ __ __

- The Development International Birth Date (DIBD) for the IMP, for the Sponsor/Sponsor-Investigator Development Safety Update Report (DSUR):
  - *<<enter DIBD>>*

The DIBD is the date of the sponsor's first authorisation to conduct a clinical study with the IMP or IMP combination

AstraZeneca will provide the Sponsor/Sponsor-Investigator with:

- The current IB and Protocol Guidelines, which identifies Olaparib AEs of Special Interest (AESIs). Section 5.4 of the IB provides details of the expectedness of AEs.

  This is only applicable when the medicinal product under study is not marketed in the country(ies) where the study is being conducted. For marketed products the local label is used and the above can be deleted.

- AstraZeneca DIBD for the IMP, for AstraZeneca DSUR:

  << enter AstraZeneca DIBD>>

3. Safety data exchange during the study

3.1 Sponsor/Sponsor-Investigator will provide AstraZeneca with:

3.1.1 Individual ICSR data

- Report unblinded Suspected Unexpected Serious Adverse Reactions (SUSARs) to AstraZeneca as individual case reports as they occur and in parallel to reporting to the regulatory authority.

  Select the appropriate bullet(s) from the list below ensuring that all other (S)AEs (both related and unrelated) are accounted for as applicable to the study type (refer to SOP Clinical Externally Sponsored Scientific Research, LDMS_001_00201128).

- Report Serious Adverse Events (SAEs) including Suspected Serious Adverse Reactions (SSARs) to AstraZeneca as individual case reports on an ongoing basis as they occur

- Report Serious Adverse Events (SAEs) including Suspected Serious Adverse Reactions (SSARs) to AstraZeneca in a blinded listing

- Promptly respond to follow up questions from AstraZeneca Data entry site

The following essential information must be provided to AstraZeneca in SUSAR, SSAR and SAE reports (initial and follow-up):

- AstraZeneca tracking number
- <<Sponsor/Sponsor-Investigator study number>>
- <<Centre number (if applicable)>>
- Patient study number
- Age
- Sex
- IMP(s) dose, start & stop date
- SAE onset & stop date
- Event term as reported by the investigator and/or the CTCAE V4 term
- <<CTCAE grade for oncology studies, as applicable>>
- Investigator's assessment of seriousness, according to ICH definitions
- Investigator's assessment of causality
- SAE Outcome
- Date of death, if applicable

Note: The Study tracking number must be provided in the header of the cover note << and also in the e-mail Subject>>. If possible the study tracking number may also be included in the (S)AE form.

3.1.2 Line listings

Line listings of SUSARs, SSARs and SAEs will:

- Be provided on a monthly basis for Phase I studies, otherwise quarterly.
- SUSARs included in the listings should be easily identifiable.
- Contain only updated information since the last listing.

Cumulative final listings will be provided at clean file for the primary analysis and after the last patient has completed the study.

3.1.3 Other safety information

- Inform AstraZeneca within 24 hours of knowledge of any emerging safety issue, unanticipated problem or actions that the Sponsor/Sponsor-Investigator is considering as a result of a safety signal with the IMP. This includes but is not limited to:
  - Urgent safety measures to be implemented in the study

- Safety amendments to protocol/patient information & informed consent
- Open reports from Independent Data Monitoring Committees (IDMCs) excluding confidential reports to IDMC and minutes of IDMC meetings
- Interactions with Regulatory Authorities (RAs)/ Ethics Committees (ECs)

- Inform AstraZeneca on an ongoing basis of any new safety trends or signals observed during routine safety surveillance activities.

This information will be included in the *quarterly* progress reports submitted to ESSROS.

- Inform AstraZeneca on an ongoing basis of any new safety trends or signals observed during routine safety surveillance activities.

3.2 AstraZeneca will:

- Provide IB updates during the course of the study.
- Immediately inform the Sponsor/Sponsor Investigator of any emerging safety issue, unanticipated problem or actions that AstraZeneca is considering as a result of a safety signal with the IMP. This includes but is not limited to:
  - New safety information which may alter the benefit risk assessment
  - Urgent safety measures to be implemented
- Request follow-up information on SUSAR, SAEs, SSARs and AESIs.
- Consult with the Sponsor/Sponsor-Investigator in the unlikely circumstance that code break information is required for an individual patient, because AstraZeneca need to expedite an SAE that has not been unblinded by the Sponsor/Sponsor-Investigator.

4. At the end of the study

At the end of the study the Sponsor/Sponsor-Investigator will:

- Provide AstraZeneca with the final study report containing details of all AEs.

5. SUMMARY OF REQUIREMENTS FOR ROUTINE EXCHANGE OF SAFETY DATA

5.1 Sponsor/Sponsor-Investigator will report safety information to AstraZeneca:

Report Type	Report format	When to send report to AstraZeneca	Method of Submission	Additional Information
SUSARs	**Individual unblinded case reports** (Initial and follow-up reports)	In parallel to submission to the concerned RA	[redacted] Or [redacted] If secure e-mail is in place.	**Sponsor/Sponsor-Investigator responsible for:** • Expedited reporting of all SUSARs to the Regulatory Authority(RA) of participating countries in line with local requirements. • Compliance with local regulations of participating countries for reporting of SUSARs to investigational sites and EC's. **AstraZeneca is responsible for:** • Reporting SUSARs to RA's where Company sponsored studies are being conducted with the IMP as appropriate or where the product is marketed. • Reporting SUSARs to Sponsor/Sponsor-investigators participating in any Company sponsored studies

				with the IMP as required by RA's.
SAEs (including SSARs)	**Individual blinded case reports** (Initial and follow-up reports)	Within 15 days from awareness of event	As above	
Report Type	**Report format**	**When to send report to AstraZeneca**	**Method of Submission**	**Additional Information**
Annual report	**Periodic safety report (**produced for external purposes e.g EC or RA of participating countries)	Only required if inconsistent with the IB/Label.	Sponsor/Sponsor-Investgator provides to ESR Coordinator. ESR Coordinator forwards to SSaMT	Examples of reports in this category include Development Safety Update Reports (DSUR) and IND update reports. Any findings that are inconsistent with the IB/Label shall be communicated to AstraZeneca during production of the report but at the latest in parallel to submission to the RA/Ethics committee.

End of Study SAEs, SSARs & SUSARs (for entry onto AZ Patient Safety database)	**A cumulative final listing** of all unblinded SAEs, SSAR's & SUSARs	At clean file* at the following time points: 1. At primary analysis 2. After last patient has completed study treatment.	 If secure e-mail is in place	AstraZeneca require a listing of all adverse events reported during the study, for the purpose of reconciliation. This list shall preferably be unblinded to also allow unblinding of the events on AstraZeneca safety database. *Clean file means when all study queries have been answered and the database is locked. For convenience and completeness SUSARs should also be included and easily identifiable.

5.2 AstraZeneca will submit the following safety information to the Sponsor/Sponsor-Investigator:

Report Type	Report format	When to send report from AstraZeneca	Method of Submission	Additional Information
SUSARs (from company sponsored studies and other sources)	**Blinded Periodic SUSAR Line Listing (PSLLs)-** ***OR*** **'No SUSAR' notification**	Six monthly	Email to Sponsor/Sponsor-Investigator *(**only** if secure dataexchange is in place),* otherwise a hard copy to be sent via mail	• In Europe these will only be provided while AstraZeneca still has patients in Company sponsored studies or until the IMP becomes marketed • AstraZeneca will provide the Company PSLLs produced for Company reporting obligations, to Sponsor/Sponsor-investigators in parallel to Company reporting to EC's and relevant RAs involved in Company sponsored studies. • Sponsor/Sponsor-Investigator will distribute these to Sponsor-investigators and ECs

				in line with local requirements.

6. CONTACT DETAILS

AstraZeneca

Study Coordinator:

Name:
Email:
Telephone:

Patient Safety Data Entry site

[redacted]

Sponsor/Sponsor-Investigator:

Periodic line listings notification:

Name:
Email:
Telephone:

SAE follow-up queries:

Name:
Email:
<<Fax>>
Telephone:

Unblinding requests:

Name:
Telephone:

AstraZeneca tracking number and IMP name(s) shall be included in email headers and secure data exchange transfer must be in place.

Information compiled by:

Signature Date

Name Title

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

A 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the investigational medicinal product (IP).

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

A 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

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

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

A 3 Identification of potential Hy's Law cases

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

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the local laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Appendix A2 for definition) by reviewing laboratory reports from all previous visits

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Appendix A2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

A 4 Follow-up

A 4.1 Potential Hy's Law criteria not met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria.

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

A 4.2 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

- Notify the AstraZeneca representative who will then inform the central Study Team

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.

- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

A 5 Review and assessment of potential Hy's Law cases

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

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 Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

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

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

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

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

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

This section is applicable to patients with liver metastases who meet PHL criteria on Study treatment having previously met PHL criteria at a study visit prior to starting Study treatment. At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the patients' condition compared with the last visit where PHL criteria were met.

- If there is no significant change, no action is required

- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team,

- 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.

A 7 Actions required for repeat episodes of potential Hy's Law

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

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

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

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection or liver disease), or did the subject meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Appendix A6A 6

If **No**: Follow the process described in Appendix A4.1.

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

If there is no significant change, no action is required.

If there is a significant change, follow the process described in Appendix A4A 4.

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

Appendix IV: Acceptable Birth Control Methods

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

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below]. This should be started from the time of registration and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

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

Acceptable Non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month after the last dose of study drug for 3 months after last dose for male patients. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception]
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD PLUS male condom. Provided coils are copper-banded

- Acceptable hormonal methods:
  - Normal and low dose combined oral pills PLUS male condom
  - Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
  - Hormonal shot or injection (eg., Depo-Provera) PLUS male condom
  - Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
  - Norelgestromin / EE transdermal system PLUS male condom
  - Intrauterine system [IUS] device (eg., levonorgestrel releasing IUS -Mirena®) PLUS male condom
  - Intravaginal device (e.g., EE and etonogestrel) PLUS male condom