Abbreviated Title: Olaparib in advanced PACC
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Title: Phase II Study of Olaparib in Subjects with Advanced Pancreatic Acinar Cell Carcinoma

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PRÉCIS

Background:

- Pancreatic Acinar Cell Carcinoma (PACC) is a rare pancreatic tumor, representing 0.5-1% of all pancreatic malignancies.
- PACC is commonly advanced at presentation and median overall survival in this population is poor.
- PACC is pathologically and biochemically distinct from pancreatic adenocarcinoma.
- No clinical trials for PACC have ever been reported.
- Patients are most commonly treated with combination regimens used for either pancreatic or colon adenocarcinoma with poor (~30%) response rates in the first-line setting.
- PACC pathological specimens demonstrate evidence of high chromosomal instability, a hallmark of DNA repair deficiency.
- Data derived from ovarian and prostate cancer patients has demonstrated that mutations in DNA repair genes can define subgroups of cancer patients with distinct vulnerabilities to DNA damage response inhibitors.
- Olaparib is a Poly-ADP ribose polymerase (PARP)-1 inhibitor that has been FDA approved for the treatment of BRCA-mutant homologous recombination repair (HRR) deficient cancers.
- As PACC has multiple hallmarks of HRR deficiency, we hypothesize that PACC will be sensitive to PARP inhibition with olaparib.
- Pre-clinical modeling of PACC has been very limited with no currently available animal models or cell lines, which precludes testing this hypothesis in the laboratory setting.

Objective:

- To assess the anti-tumor activity of single agent olaparib, a PARP inhibitor, in participants with advanced pancreatic acinar cell carcinoma (PACC)

Eligibility:

- Participants must have advanced previously treated PACC
- Age ≥18 years
- Adequate organ and bone marrow function

Design:

- This is a phase II, single arm, single center study of olaparib in participants with advanced previously treated PACC.
- All participants will take olaparib by mouth twice daily for up to two years or until disease progression or intolerable side effects.
- Participants will be assessed for safety (continuously) and efficacy (every 8 weeks).
- Up to 13 evaluable participants will be enrolled.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To assess the anti-tumor activity of single agent olaparib, a PARP inhibitor, in participants with advanced pancreatic acinar cell carcinoma (PACC)

1.1.2 Secondary Objectives

- To assess alternative measures of anti-tumor efficacy such as clinical outcomes and blood biomarkers
- To assess the safety of olaparib in advanced PACC

1.1.3 Exploratory Objectives

- To acquire tumor tissue through research biopsies that can be used to establish new patient-derived xenografts (PDX), cell line and organoid models of PACC
- To assess genetic alterations in PACC through genetic mapping techniques (gene copy number analyses and cytogenetics) and to evaluate alterations in homologous recombination repair (HRR) and other DNA repair pathways
- To assess alterations in mRNA and protein levels of HRR-related genes such as *BRCA1/2*, *PALB2* and *RAD51*, and functionality of HRR pathway as predictive biomarkers for olaparib
- To assess ID3 protein levels and protein levels of DNA repair pathway genes of interest in participant tumor and normal tissue
- To assess relationship of treatment response to tumor profile

1.2 BACKGROUND AND RATIONALE

1.2.1 Pancreatic Acinar Cell Carcinoma (PACC)

PACC is a rare pancreatic tumor that accounts for 0.5-1% of all pancreatic malignancies [1]. There are estimated to be 250-500 cases diagnosed in the United States each year. More than half of patients present with advanced disease and are not candidates for surgical resection. Metastases are most often located in the liver (78%) [2, 3]. Recent retrospective case series have reported a median overall survival (OS) in this population of 15-20 months [2, 4]. PACC patients who present with resectable disease have a median overall survival that approaches or exceeds 5 years. Unfortunately, almost half of patients who present with localized disease and receive surgery will have recurrence [1, 2, 5, 6]. Positive lymph node status and perineural invasion are predictive of recurrence. Recurrence almost always manifests as hepatic metastases. In summary, ~75% of patients who are diagnosed with PACC will develop metastatic disease, most typically to the liver.

PACC is pathologically distinct from pancreatic adenocarcinoma [7]. Under the microscope, PACC is a highly cellular tumor with little stromal response. Over 90% of tumor cells stain positive for trypsin and chymotrypsin. Significant serum CA 19-9 elevation is uncommon, while elevation of serum lipase is observed in at least 50% of patients, and elevations in alpha-fetoprotein (AFP) can also be seen in some cases. Those with very high lipase levels (>1000 u/dL) can develop fat necrosis and panniculitis from lipase hypersecretion syndrome which manifests as painful, erythematous subcutaneous nodules accompanied by polyarthralgia and eosinophilia [8]. Mixed acinar-ductal and mixed acinar-endocrine variants represent about ~10% of cases, and the acinar component forms the majority of cells in almost all cases. These tumors behave similarly to pure PACC but acinar-ductal tumors may express mucin and acinar-neuroendocrine tumors chromogranin and/ or synaptophysin in addition to exocrine enzymes [7].

No clinical trials for PACC have ever been reported. There is no standard therapy for this disease. All information about response to systemic treatments comes from retrospective studies [2, 4, 9]. PACC patients are most commonly treated with regimens used for either pancreatic or colon adenocarcinoma. Clinical responses to single agent chemotherapy are rare [9, 10]. Recent studies suggest that the response rate to first-line combination chemotherapy is 30% or less. Regimens containing a platinum salt with a fluoropyrimidine appear to have the most clinical benefit. The benefit of gemcitabine in this disease is debatable [4].

1.2.2 Pre-clinical models of PACC

Pre-clinical modeling of PACC has been very limited. A rat model was described in 1980, but cells grown in culture rapidly lost their differentiation within a few passages [11]. A patient-derived xenograft derived from a PACC patient liver biopsy was recently described [12]. This model was found to be sensitive to oxaliplatin, and resistant to other chemotherapy typically used to treat PACC including 5-fluorouracil, irinotecan, gemcitabine, erlotinib and doxorubicin. Sequencing identified an inactivating BRCA2 mutation. A cell line derived from a patient with acinar cell carcinoma was also reported [13], but no characterization for PACC markers lipase, trypsin or chymotrypsin was performed. In addition, almost no chromosomal gains or losses were identified, raising doubt that this is truly a PACC line. One of the scientific goals of the proposed study is to acquire tumor tissue through research biopsies that can be used to establish new patient-derived xenograft (PDX), cell line and organoid models of PACC.

1.2.3 Molecular characteristics of PACC tumors

Molecular characteristics of PACC tumors have suggested that they are DNA repair deficient. Three different studies have performed detailed genomic analysis of PACC patient tumor tissue [14-16]. All 3 studies agreed that no gene was mutated in >30% of tumors. Results showing frequent mutation (10-25% incidence) of a gene in one of these studies (e.g., JAK1) could not be replicated in the cohorts tested in the other studies. Activating BRAF gene fusions were identified in ~20% of patients in one study [14]. Two of these studies [15, 16] and an additional, earlier study using comparative genomic hybridization to examine chromosomal changes [17] found frequent copy number alterations indicative of high chromosomal instability, a hallmark of DNA repair deficiency. In addition, mutational signature analysis identified the defective DNA repair signature in 15 of 22 tumors analyzed [15]. Mutations in known DNA repair genes, DNA polymerases and spindle checkpoint genes could not account for this finding [16]. BRCA1/2 mutation does occur in PACC but at rates <10%, so cannot account for the high rates of DNA repair deficiency. Jäkel et al. performed epigenomic analysis to find methylation changes between tumor and normal tissue and then overlaid these changes upon maps of copy number alterations to identify 292 genes most likely to have decreased expression at the protein level in PACC [15]. Immunohistochemistry (IHC) analyses for 8 of these was performed on patient tumor tissues (n = 23 in Cohort 1, n = 39 in Cohort 2) and revealed frequent downregulation of 4 of these genes: ID3 (in 89-94% of tumor samples), ARID1A (in 68-74%), APC (in 62-71%) and CDKN2A (in ~51%) [15]. Verification of decreased protein levels for the other 284 genes predicted to be down-regulated at the protein level (including DNA repair-related genes [18] APITD, GADD45A, HFM1, HMGB2, MAD2L2, MUTYH, NEIL3, PLK3, RAD54L, RPA2, SMARCAD1, TCEB3, USP1) have not yet been reported. While ARID1A has long been known to participate in DNA repair, a 2017 report identified ID3 as a critical player in the DNA double strand break repair pathway. Specifically, it was reported that ID3 was required for recruitment of MDC1 to sites of DNA damage, and loss of ID3 resulted in profound impairment of HRR following ionizing radiation [19]. Based on these data, we hypothesize that some PACC tumors may be HRR deficient due to the nearly ubiquitous reduction in ID3. Subsequently, additional information has emerged confirming that ID3 plays a significant role in HRR. Bakr and colleagues found that ID3 affects DNA repair via at least two different mechanisms: 1) direction interaction with DNA double strand break (DSB) repair proteins including early complex members NBS1 and RAD50 and interaction with RECQL to facilitate RAD51 loading, and 2) transcriptional changes in HRR and Fanconi Anemia pathway genes following exposure to ionizing radiation [20]. Both of these processes were independent of MDC1. In addition, we have shown that ID3 knock-down increases DNA damage [21]. HR deficiency seen in PACC may be secondary to downregulation of ID3 due to its novel role in DDR processes.

1.2.4 Poly-ADP ribose polymerase (PARP)-1 inhibitors in HRR deficient cancer

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

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious

DSBs during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by HRR.

Several PARP inhibitor drugs, including olaparib, have now been FDA approved for the treatment of BRCA-mutant HRR deficient cancers after demonstrating clinical benefit in patients with breast and ovarian cancers bearing these mutations [22-24]. They have also shown efficacy in BRCA mutant prostate and pancreatic adenocarcinoma [25, 26]. The combination of PARP inhibition with BRCA-mutation is synthetically lethal. PARP inhibitors prevent efficient DNA SSB repair and also trap the PARP enzyme on these sites of broken DNA causing a "roadblock" against progression of the DNA replication machinery. This stalls the replication fork and generates a DNA DSB. While normal cells can use HRR to fix this lesion, BRCA-mutant cells cannot efficiently make this type of repair. This synthetic lethal interaction between BRCA mutation and PARP inhibition underlies the therapeutic efficacy of these drugs in HRR deficient tumors [27, 28]. PARP inhibitors are currently being tested for clinical efficacy against tumors bearing mutations in genes other than BRCA-1 and BRCA-2 that are important in the HRR pathway.

Recently, it was shown that decreased levels of ID3 confer increased sensitivity to PARP inhibition [20]. Cell lines of the same cancer type with lower expression of ID3 had increased sensitivity to PARP inhibition. Also, knock-down or knock-out of ID3 also resulted in increased anti-tumor efficacy of PARP inhibition in prostate, PDAC, and osteosarcoma cell lines.

Multiple clinical studies have demonstrated that sensitivity of BRCA mutant tumors to PARP-1 inhibitor therapy correlates with sensitivity to platinum-based chemotherapy agents. This has been best demonstrated in ovarian cancer patients where treatment with olaparib monotherapy resulted in objective response rate (ORR) (CR + PR) of 61.5% (8 of 13) in platinum sensitive patients, 41.7% (10 of 24) in platinum resistant patients, and 0% (0 of 13) platinum refractory patients [29] (26). Other studies have also reported decreased response to PARP inhibition therapy in platinum-insensitive patients [30]. Reactivation of the HRR pathway through BRCA reversion mutation, increased RAD51 loading, or 53BP1 loss to initiate BRCA-independent HRR are cited as the most common platinum-resistance mechanisms. PARP inhibition ceases to be lethal once these changes occur.

Direct data examining whether platinum-resistant disease with ID3 deficiency harbors similar resistance to PARP inhibition is unavailable. Because ID3 deficiency effects multiple events in the HRR pathway and also transcription of HRR pathway components, adaptations that render cells resistant to platinum may be insufficient to eliminate ID3-conferred PARP sensitivity. Notably, ID3 knock-down in the MIA-PACA PDAC cell line confers increased sensitivity to PARP inhibitor therapy [20] but fails to alter platinum sensitivity [21]. It is currently unclear whether platinum resistance is predictive of resistance to PARP inhibition in ID3-deficient tumors like PACC.

1.2.5 Rationale for treating PACC with olaparib

PACC has multiple hallmarks of an HRR deficient tumor: frequent sensitivity to platinum-based chemotherapy regimens, high chromosomal instability, mutational signature of DNA damage repair deficiency, and almost universal downregulation of a gene suggested to be involved in HRR (ID3). Many HRR deficient tumors are sensitive to PARP inhibitors. Therefore, we hypothesize that PACC will be sensitive to PARP inhibition with olaparib. Since there are no appropriate pre-clinical models of PACC, this precludes us from testing our hypothesis in the laboratory setting.

Therefore, we propose to initiate a small Phase 2 study using olaparib to treat participants with PACC.

This study utilizes the same doses of olaparib and route of administration which have been previously approved for other indications. PARP inhibitors have a well described side effect profile that has not varied significantly amongst the different tumor types where it has previously been tested. These toxicities include increased rates of primarily low-grade nausea, fatigue, headache, arthralgia, diarrhea, constipation, dysgeusia, and anorexia, as well as anemia, neutropenia and thrombocytopenia, and venous thromboembolism which can be severe in some patients [22-25]. Olaparib treatment increases the risk of acute myelogenous leukemia or myelodysplastic syndrome. A recent metanalysis found that PARP inhibitor treatment doubles the risk of developing these hematologic malignancies from 0.48% to 0.73% with a mean latency since first drug exposure of 17.8 months [31]. We do not anticipate a differing toxicity profile when using olaparib in the PACC population from what has been seen previously for other populations of patients with advanced HRR deficient tumors.

Because there are no standard treatments approved for PACC and the safety of olaparib is well described, the proposed study constitutes a rational initial step to identify a targeted treatment regimen effective against PACC.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Histological or cytological diagnosis of pancreatic acinar cell carcinoma (PACC) as confirmed by NIH Laboratory of Pathology (LP).

2.1.1.2 Participants must have received one prior line of combination chemotherapy (or be ineligible to receive combination chemotherapy) with tumor still not amenable for potentially curative resection or be ineligible to receive combination chemotherapy. There is no limit on the number of prior therapies.

2.1.1.3 Access to medical records from past treatment

2.1.1.4 Measurable disease, per RECIST 1.1. See Section **6.3** for the evaluation of measurable disease.

2.1.1.5 Age ≥18 years.

2.1.1.6 Eastern Cooperative Oncology Group (ECOG) performance status ≤1 (see **Appendix A-Performance Status Criteria**).

2.1.1.7 At least 3 weeks from previous chemotherapy or radiation therapy prior to planned start of treatment.

2.1.1.8 At least 30 days or 5 half-lives (whichever is greater) since receipt of any investigational therapy prior to planned start of treatment.

2.1.1.9 Fully recovered from all reversible sequalae and ≥2 weeks from major surgery or from minor surgical procedure such as biliary or duodenal stenting prior to planned start of treatment.

2.1.1.10 At least 2 weeks since last use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat,

indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil).

2.1.1.11 At least 5 weeks since last use of phenobarbital, enzalutamide, and at least 3 weeks since last use of other strong (e.g., phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate (e.g., bosentan, efavirenz, modafinil) CYP3A inducers.

2.1.1.12 Adequate organ and marrow function as measured within 28 days prior to study treatment as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– hemoglobin	≥10 g/dL with no blood transfusion within the last 28 days
– platelets	≥100,000/mcL
– total bilirubin	within 1.5x normal institutional upper limit of normal (ULN)
– Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT)	≤ institutional ULN unless liver metastases are present in which case they may be ≤5x ULN
– Creatinine	must be within normal range, OR ≥51 mL/min per the formula below)* or measured by 24-hour urine test
*Estimated creatinine clearance =	$\frac{(140-\text{age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72^{a}}$ (x F), where F=0.85 for females and F=1 for males

This list includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

2.1.1.13 The effects of olaparib on the developing human fetus are unknown. For this reason and because PARP inhibitor agents are known to be teratogenic, individuals of child-bearing potential (IOCBP) and individual able to father a child must agree to use adequate contraception prior to study entry and for the duration of study participation. Specifically, see **Appendix B- Acceptable Birth Control Methods**.

2.1.1.14 Participants must agree to abstain from consuming grapefruit juice throughout the duration of study treatment with olaparib.

2.1.1.15 Ability of participant to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 History of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib.

2.1.2.2 Participants unable to swallow orally administered medication or suffering from gastrointestinal (GI) disorders likely to interfere with absorption of study medication.

2.1.2.3 Participants with human immunodeficiency virus (HIV) are excluded even if viral load (VL) is undetectable.

2.1.2.4 Active hepatitis B (HBV) or hepatitis C virus (HCV)

2.1.2.5 Resting electrocardiogram (ECG) indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or participants with congenital long QT syndrome.

2.1.2.6 Recent (within 3 months) myocardial infarction

2.1.2.7 Unstable angina pectoris

2.1.2.8 Symptomatic congestive heart failure

2.1.2.9 Uncontrolled major seizure disorder

2.1.2.10 Superior vena cava syndrome

2.1.2.11 Extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan

2.1.2.12 Psychiatric illness/social situations (within the last 3 months) that would limit compliance with study requirements or prohibits obtaining informed consent.

2.1.2.13 Uncontrolled intercurrent illness or participants considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active uncontrolled infection as documented in prior records or suggested by medical history, physical examination or standard clinical assessments such as imaging and laboratory studies.

2.1.2.14 Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or with features suggestive of MDS/AML.

2.1.2.15 Solid or liquid malignancy other than PACC unless curatively treated with no evidence of disease for ≥5 years, except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma.

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

2.1.2.17 Participants who are nursing and unwilling to stop.

2.1.2.18 Symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. Brain metastases are considered uncontrolled if the dose of corticosteroid being provided for control of brain metastases has been titrated in the 4 weeks prior to start of treatment.

2.1.2.19 Participants with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for ≥28 days. Participants with unstable spinal cord compression are ineligible even if previously treated.

2.1.2.20 Participants with large volume ascites, serum albumin <2.5 mg/dL, or having received paracentesis within the last 4 weeks.

2.1.2.21 Participants with persistent toxicities >Grade 2 or with new Grade 2 events within the last 2 weeks per Common Terminology Criteria for Adverse Event (CTCAE) version 5 caused by previous cancer therapy.

2.2 RECRUITMENT STRATEGIES

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms. Subjects will also be drawn from patients seen in OP12 Medical Oncology clinic at the NIH Clinical Center as well as from referrals from outside providers.

2.3 SCREENING EVALUATION

2.3.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the participant has signed a consent include the following:

- Email, written, in person or telephone communications with prospective participants
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

2.3.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the participant has signed the consent on this study. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

All necessary laboratory values and assessment reports must be available and reviewed prior to signing study consent for treatment.

The following will be completed as part of screening:

2.3.2.1 Performed at any time prior to treatment initiation

- Confirmation of histologic or cytologic diagnosis of PACC by the NCI LP. If archival tissue is unavailable or insufficient for this purpose, a fresh biopsy will be collected.

2.3.2.2 Performed within 28 days prior to treatment initiation

- Medical history including prior cancer therapies, surgical history, history of blood transfusions
- Physical exam including vital signs and ECOG performance status (see **Appendix A-Performance Status Criteria**)
- Computer tomography (CT) scan with contrast of chest, abdomen and pelvis (CAP) and areas of known or suspected disease involvement; F-fluorodeoxyglucose positron emission tomography (FDG-PET) or magnetic resonance imaging (MRI) may also be performed when clinically indicated as per the primary investigator's discretion.
- Hematology including blood smear (Complete blood count [CBC] with differential)
- Acute care panel (sodium, potassium, chloride, bicarbonate, creatinine, glucose, blood urea nitrogen [BUN])
- Hepatic panel (alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin)

- Mineral panel (albumin, calcium, magnesium, phosphorus)
- Coagulation panel (prothrombin time [PT], partial thromboplastin time [PTT]): Activated partial thromboplastin time (aPTT)
- HIV antigen/antibody testing
- Hepatitis B surface antigen (HBsAg) and HCV with reflex viral load
- Urinalysis
- Serum or urine human chorionic gonadotropin (β-hCG) in IOCBP
- ECG

2.4 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.4.1 Screen failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of reversible factors (e.g., biliary congestion amenable to decompression, recent thrombotic event, active infection requiring systemic treatment, low blood counts due to recent chemotherapy, pregnancy, or transient social issues that would impact compliance) may be rescreened.

2.4.2 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Cohort 1	Pancreatic acinar cell carcinoma

Arms

Number	Name	Description
1	Arm 1	Olaparib, taken orally, twice daily

Arm Assignment

Participants in Cohort 1 will be directly assigned to Arm 1.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

- This is a Phase 2, open label, single center study of olaparib in participants with previously treated PACC.
- A fixed dose of olaparib will be given orally continuously twice daily for 28-day cycles.
- Olaparib will be continued for up to 2 years or until disease progression, unacceptable toxicity, or another off-treatment reason is met (see Section **3.9.1**).

3.2 DRUG ADMINISTRATION

Olaparib at the dose of 300 mg will be given orally continuously twice daily, with doses taken at approximately the same times each day 12 hours apart. Three tablets of 100 mg or two tablets of 150 mg should be taken with approximately 240 mL of water. Doses may be taken with a light meal/snack. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

Olaparib will be dispensed at the start of each 28-day cycle. Per the CCR policy for self-administered oral investigational agents which will be followed in this protocol, participants will be provided with a pill diary (**Appendix C- Participant Optional Olaparib Pill Diary**), instructed in its use, and asked to bring it with them to each appointment.

Participants should be given clear instructions on how and when to take their study treatment. Participants will self-administer olaparib. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate source document (e.g., medical record). All participants must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Participants will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the participant on their participant diary (if completed) and by the site staff in the source documents.

If a participant misses more than 25% of olaparib doses during any cycle due to medical issues unrelated to drug toxicity:

- If the drug hold is less than 4 weeks, then the participant should resume study treatment when recovered. The length of the cycle should be extended to allow the participant to complete at least 21 days of olaparib treatment within the current cycle before starting Day 1 of the next cycle. If this occurs during Cycle 1 and the drug is held for longer than 7 days, new baseline staging scans should be obtained prior to restarting the drug if the participant had received 7 days of olaparib or less and the baseline scans were performed four weeks or more from the time drug is restarted.
- If the drug hold is greater than 4 weeks:
    - During Cycle 1, the participant will be considered inevaluable for response, will be replaced, and will be taken off study treatment.
    - During Cycle 2 or beyond, the participant will be taken off study treatment, but will not be replaced or made inevaluable due to missed olaparib doses.

See Section **10.3** f or additional information.

Participants must return all containers and any remaining tablets at the end of the study.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all the intact tablets can be seen and counted. Should any participant 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 participant 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 should not be taken, and the participant should take their allotted dose at the next scheduled time.

It is prohibited to consume grapefruit juice while on olaparib therapy, due to P450 interactions.

3.3 DOSE MODIFICATIONS

Olaparib dosages will be modified as described and published previously for the POLO trial (NCT02184195, "A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum-Based Chemotherapy"). The relevant information is included in **Appendix D- Management of Toxicity of Olaparib**.

For guidance on dose reductions for management AEs (including renal impairment) refer to **Table 1** and **Table 2**.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see **Table 3**.

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

Table 1: Dose reductions for study treatment to manage adverse events

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

Table 2: Dose reduction for study treatment if participant develops moderate renal impairment

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

Table 3: Dose reductions for study treatment if participant has to start taking a strong or moderate CYP3A inhibitor

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

3.4 ON STUDY ASSESSMENTS/EVALUATIONS

3.4.1 Timing of procedures

The following describes all tests and procedures to be conducted during the study and during the treatment. Refer to Study Calendar (Section **3.7**) for timing and applicable windows.

For each time period, consider the following order of assessments:

- **Screening:** Refer to Section **2.3.2**.
- **Baseline/Cycle 1**: The results of all assessments must be available and reviewed prior to initiation of olaparib administration to ensure results still meet standards defined in eligibility criteria. All participants are required to complete baseline evaluations per the Study Calendar (Section **Error! Reference source not found.**) within 7 days prior treatment initiation except for imaging assessments that are required to be done 21 days prior to treatment initiation and pregnancy test that is required to be done within 3 days prior to treatment initiation. Any screening tests performed within the specified time frame for baseline do not need to be repeated.
- **Cycle 1 Day 8 and Day 15:** The results of CBC with differential, acute, mineral, and hepatic panels, and tumor markers must be available and reviewed within 2 calendar days of the blood draw. Components of these panels that are specifically relevant to monitoring the effects of olaparib are specified in "Clinical laboratories relevant to research" later in this section. The remaining laboratory values collected on these panels are part of standard of care assessments and unrelated to research.
- **Subsequent Cycles:**
    - Each cycle is 28 days
    - Pre-cycle assessment may be done up to 7 days prior to the start of the cycle or by 7 days after the planned start of the cycle if the participant has sufficient olaparib doses to continue the prescribed treatment. The cycle length is not changed if the "pre-cycle" assessment is performed late or early.
    - The results of all assessments with the exception of serum tumor markers and ECG must be available and reviewed prior to initiation of olaparib administration in a new cycle to confirm eligibility for ongoing treatment administration.
- **Unscheduled Visits:** In the event of an unscheduled/unplanned visit (e.g., additional clinical assessment(s) due to toxicity), the investigator should use best clinical judgement as to the necessary assessments. In the event that the decision is made to continue treatment, all tests/assessments as required by the next visit on the Study Calendar (Section **3.7**) should still be conducted (or repeated) within the applicable windows. If a decision is made

to discontinue treatment, the participant should move to the End of Treatment visit (Section **3.5**), with tests/assessments completed (or repeated) within the applicable windows.

- **Remote/Telehealth Visits:** If participants are unable to travel to the Clinical Center for assessment during a specified window(s) due to extenuating circumstances such as illness, travel restrictions, inclement weather, etc., every effort should be made for the participant to complete the required evaluation with their local medical provider. Any unexpected or planned remote visit with participants will follow institutional approved remote platform requirements used in compliance with local policy (e.g., including NIH HRPP Policy 303).

  Given the standard nature of the planned clinical laboratories, interlaboratory variability is not a concern and participants may have clinical labs drawn locally, with results sent to the NIH study team (e.g., via fax); in these cases, an appropriate member of the study team will follow-up remotely to discuss any symptoms and to make recommendations/adjustments, as necessary. Additional study drug will not be provided to a study participant until the specified assessments have been performed.

3.4.2 Description of Procedures

The following is a description of all procedures:

- Symptom assessment: verbal review of participant's current symptoms pertaining to eligibility on study.
- Medical history: a review of treatment history, any ongoing medical conditions, and medical history pertaining to eligibility on study
- Physical exam to determine eligibility and establish a baseline, including vital signs and weight: review of organ systems, weight (kg), and vital signs (i.e., temperature, pulse, respirations, blood pressure). After initiation of study drug, symptom-directed physical examinations will be performed as clinically indicated in the investigator's judgment.
- Performance status (ECOG): an assessment of activities of daily living; see **Appendix A- Performance Status Criteria** to assess safety, eligibility and to determine continuation of treatment per Section **3.3**.
- Laboratory assessments: The following comprises the required tests/analytes. These assessments may be performed at CLIA (or equivalent) certified laboratories outside the Clinical Center and results forwarded to the study team for review and management. Given that the methodologies utilized are similar across all laboratories, no significant variability is expected and there is no anticipation that study data will be affected. Note: Panels containing the tests below may be ordered in lieu of individual tests.
  - CBC with differential panel
  - Acute care, mineral, and hepatic panels: Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, Alkaline Phosphatase, ALT, AST, Total Bilirubin, Direct Bilirubin, Albumin, Calcium,

    Note: In case a participant shows an AST **or** ALT ≥ 3xULN together with total bilirubin ≥2xULN, please refer to **Appendix E- Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law**, for further instructions.

- Coagulation panel (PT, PTT): Please note that participants taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then at the start of every cycle if the INR is stable. Each coagulation test result will be recorded in CRF.
- Urinalysis: protein, specific gravity, glucose, and blood
- Pregnancy test: Serum or urine β-HCG for IOCBP
- Serum tumor markers: Appropriate tumor markers to follow PACC include lipase, amylase, and/ or AFP. All three markers will be collected at baseline and end of treatment. Only those found to be elevated at baseline will be collected on Day 1 of subsequent cycles. If a participant's tumor is known (from prior medical records) to make a marker not listed here, this should also be measured at baseline, the start of each cycle and at end of treatment.

- Imaging scans performed for eligibility determination and response assessment: CT scans (including CAP); may be adjusted to assess additional known sites of disease, as needed. Performed every 8 weeks (+ 7 days) (e.g., from/at end of cycle 2 and every even numbered cycle thereafter). If radiologic response to treatment is observed (see Section **6.3**), confirmatory scans may be performed at 4-week interval, and in this case subsequent scans should continue prior to every other cycle thereafter (i.e., end of every odd numbered cycle). In the case of scheduling delays, dose holds, etc., response assessments should continue every 8 weeks (+ 7 days).
- Adverse events: Adverse events (assessed using the NCI CTCAE v5.0) will be continuously monitored throughout the study until 30 days after the last dose of olaparib or start of new anticancer treatment, whichever comes first. Adverse events that occur beyond 30 days after the last administration will be recorded as noted in Section **6.1**.
- Review of concomitant medications: Concomitant medications will be collected throughout the study until 30 days after the last dose of the study drugs or start of new anticancer treatment, whichever comes first.
- Olaparib administration, including dispensing and adherence review: Study drug will be dispensed at each cycle and instructed to be self-administered by participants per schedule- see Section **3.2**. Participants may be given an optional dosing diary (see **Appendix C- Participant Optional Olaparib Pill Diary**); that may be reviewed at each noted visit for drug adherence/accountability.
- Contraception review: Review of contraception to assess eligibility and to determine continuation of treatment See **Appendix B- Acceptable Birth Control Methods**.
- Correlative research samples: Refer to Section **5**.

3.5 End of Treatment Assessments

The participant will continue on study drug for up to 2 years or until there is evidence of tumor progression, intolerable toxicities, or withdraws from treatment (refer to Section **3.9.1**). The "End of Treatment" assessments (Section **3.7**) will be performed 14-30 days after completing the last dose of study drug or before the initiation of a new anti-cancer treatment, whichever comes first.

If the participant cannot return to the study center for this visit, the participant may complete assessments locally, including seeing a local physician for a physical exam and local clinical laboratories, and the study team will follow-up with the participant remotely. Imaging scans need only be performed at end of treatment, if not performed within the last 4 weeks.

3.6 FOLLOW-UP PERIOD

3.6.1 30-day Follow-up Visit

The mandatory Safety Follow- up visit should be conducted approximately 30 (+ 5 days) after the last dose of study drug and before initiation of a new anti-cancer treatment, whichever comes first (see assessments, Section **3.7**). In addition, the study team will confirm contact information for participant and a designated family member and remind participant of follow-up contact that will be conducted for survival status.

3.6.2 Post-Therapy Follow-up

Overall survival will be collected until 1 year post-last dose of olaparib. Participants will be contacted remotely, (e.g., phone or email) approximately every 90 days. If participants are still being seen at the NIH, this information may be obtained from the medical records.

3.7 STUDY CALENDAR

1 cycle = 28 days

Procedure	***Screening***	***Cycle 1***		***Subsequent Cycles***	***End of Treatment***	***Follow-up***	
		Baseline/ D1	***D8 and D15***	***D1***		***30-day Follow-up***	***Post Therapy Follow-up***
Window(s):	Section 2.3.2	Section **Error! Reference source not found.**	Section 3.4.1		Section 3.5	Section 3.6.1	Section 3.6.2
	≤ 28 days	*≤ 7 days*	*± 3 days*	*± 7 days*	*14-30 days after last treatment*	*+5 days*	*~ q90 days for 1 year post treatment*
Informed consent	X						
Medical and surgical history	X	X		X	X	X	
Confirmation of diagnosis/biopsy	X[2]						
Physical exam	X	X		X	X		
Vital signs, weight	X	X		X	X		
Performance status	X	X		X			
Symptom assessments/Adverse events		X		X		X	
Concomitant medications		X		X		X	
Review contraception	X					X	
Ongoing survival assessment by phone, email, or other NIH remote platform							X
Clinical laboratories							
CBC with differential	X	X	X	X	X		
Chemistry panels (acute, hepatic, and mineral)	X	X	X	X	X		

Procedure	***Screening***	***Cycle 1***		***Subsequent Cycles***	***End of Treatment***	***Follow-up***	
		Baseline/ D1	***D8 and D15***	***D1***		***30-day Follow-up***	***Post Therapy Follow-up***
Window(s):	Section **2.3.2**	Section **Error! Reference source not found.**	Section **3.4.1**		Section **3.5**	Section **3.6.1**	Section **3.6.2**
	≤ 28 days	*≤ 7 days*	*± 3 days*	*± 7 days*	*14-30 days after last treatment*	*+5 days*	*~ q90 days for 1 year post treatment*
Tumor markers		X		X	X		
HIV testing	X						
HBsAg and HCV with reflex viral load	X						
Coagulation panel (PT, PTT)	X	X		X			
Urinalysis	X	X					
Serum or Urine β-hCG	X	X		X	X	X	
Radiology/ Other Assessments							
ECG	X						
CT CAP	X	X[1]		X *Every 8 weeks*			
Study Drug							
Dispense olaparib		X		X			
Olaparib administration		*Continuous PO BID daily dosing*					
Review Participant Dosing Diary and Drug Accountability (optional)		X		X			
Correlative Research		See Section **5.3**					
PBMCs		X					

Procedure	***Screening***	***Cycle 1***		***Subsequent Cycles***	***End of Treatment***	***Follow-up***	
		Baseline/ D1	***D8 and D15***	***D1***		***30-day Follow-up***	***Post Therapy Follow-up***
Window(s):	Section **2.3.2**	Section **Error! Reference source not found.**	Section **3.4.1**		Section **3.5**	Section **3.6.1**	Section **3.6.2**
	≤ 28 days	*≤ 7 days*	*± 3 days*	*± 7 days*	*14-30 days after last treatment*	*+5 days*	*~ q90 days for 1 year post treatment*
Tumor Biopsy (optional)		X		X *(once only, C2 preferred)*	X		
Archival Tissue (optional)		X					

1. *Only if done >21 days prior to initiation of study therapy*
2. *Any time prior to treatment initiation*

Note: Other tests/assessments should be completed as clinically indicated. For a description of all on study assessments, see Section **3.4**.

3.8 COST AND COMPENSATION

3.8.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs.

3.8.2 Compensation

Participants will not be compensated on this study.

3.8.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete an end of treatment visit approximately 14-30 days following the last dose of study therapy (see Sections **3.5** and **3.7**).

3.9.1 Criteria for removal from protocol therapy

- Progressive disease
- Participant requests to be withdrawn from active therapy
- Requires use of prohibited medication (see Section **4.2**)
- Unacceptable toxicity as defined in Section **3.3**
- Investigator discretion
- Participant non-compliance (e.g., misses >25% of doses of olaparib in any cycle)
- Positive pregnancy test

3.9.2 Off-Study Criteria

- Screen failure
- Completed study follow-up period
- Participant lost to follow-up
- Participant requests to be withdrawn from study
- Investigator discretion
- Death
- The study is discontinued

3.9.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for two (2) scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within two (2) weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

Note: A regularly updated source such the one available at http://medicine.iupui.edu/CLINPHARM/ddis/clinical-table should be consulted for complete listing of CYP3A interactions.

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

4.1 SUPPORTIVE CARE

Unless otherwise indicated in Section **3.3**, toxicities will be managed per current evidence-based practice guidelines in consultation with a medically responsible investigator if available.

4.2 PROHIBITED MEDICATIONS

No other anti-cancer therapy (e.g., chemotherapy, immunotherapy, hormonal therapy [hormone replacement therapy (HRT) is acceptable], radiotherapy [unless palliative – see Section **4.3.2**], biological therapy or other novel agent) is to be permitted while the participant is receiving study medication. (Note: Participants may continue the use of bisphosphonates or denosumab for bone disease provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.)

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

Strong or moderate CYP3A inhibitors or inducers (**Table 4**) should not be taken with olaparib. If no suitable alternative, then dose of olaparib should be reduced (see **Table 3**).

Table 4: 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 participant's safety and welfare this could diminish the clinical efficacy of olaparib. If a participant requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of olaparib.

Table 4: 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.

4.3 PERMITTED MEDICATIONS & TREATMENTS

4.3.1 Anticoagulant Therapy

Participants who are taking warfarin should be transitioned to another anticoagulant therapy for the duration of participation in this protocol, such as subcutaneous heparin.

4.3.2 Palliative Radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bone 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 participant undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

Refer to Section **5.3** for sample collection and timepoints.

5.1.1 Blood

Blood samples will be collected and processed according to validated standard operating procedures (SOPs) to maintain sample quality and participant confidentiality.

5.1.1.1 PBMCs

Participant PBMCs (matched to tumor) will be stored for making of syngeneic humanized models if these are required for experimental drug testing. If PBMCs are not needed for this purpose, they may be utilized for immune monitoring.

5.1.2 Tumor Tissue (Fresh/Recent archival)

Tumor tissues (either biopsy or archival tissue) will be collected at screening. If no archival tissue is available, participants will be required to undergo a biopsy to confirm cancer diagnosis.

Participants may elect to provide tissue for additional research studies described below designed to better understand the treatment effect of olaparib on their tumor. Participants will be provided with the following options to provide tumor tissue for the analyses described below:

1. Participants who have had recent core or excisional biopsy of a tumor lesion (within 90 days prior to Cycle 1/Day 1 and since completion of last anti-cancer therapy) may consent to use this tissue for baseline analysis for the purposes of this study even if it was collected for another reason.
2. Participants may consent to undergo new interventional radiology guided needle biopsies of a tumor lesion for research purposes unless tumor is considered inaccessible or biopsy is otherwise considered not in the participant's best interest. Core needle biopsies (1-3 cores) with cross sectional imaging will be obtained per routine standard of care by an Interventional Radiologist, typically by using a 16-18G needle at the discretion of the provider performing the procedure. Research biopsies will be performed under local anesthesia and conscious sedation may be used, if warranted, and the use and risks are acceptable to the participant. As CT guidance will be used for a research biopsy procedure, research radiation exposure will be discussed with the participant. The participant will be reminded that all sampling for research is voluntary. No more than 3 optional research biopsies will be performed on this protocol for research purpose only. Consent for biopsy will be obtained by the interventionalist at the time of the procedure. If the participant refuses the optional biopsy, the refusal will be documented in the medical record.

5.2 PLANNED ANALYSES

Note: Platforms and procedures may be adjusted based upon current technology and/or collaborations in place at the time of actual analyses.

5.2.1 ATAC-seq

This analysis will be performed to determine epigenetic patterns in PACC as compared to normal acinar cells and to determine whether olaparib treatment changes baseline epigenetics of PACC. Coded, linked samples will be provided to the Arda Lab for this analysis.

5.2.2 Single cell RNA analysis

We will use this technique to identify the different types of cells present in PACC tumors at baseline and following treatment with olaparib. Coded, linked samples will be provided to the Arda Lab for this analysis.

5.2.3 Cytogenetics

Copy number changes in individual cells will be assessed by fluorescence in situ hybridization (FISH). Coded, linked samples will be provided to the Reid Lab for this analysis.

5.2.4 Assessment of HR pathway gene mutation status

Mutations in common HR genes will be assessed through Laboratory of Pathology COMPASS program. CLIA-certified analysis of mutation in ~500 oncogenes including many HR pathway genes is included in this analysis. More detailed sequencing (WES or WGS) may be performed through 19C0016 Natural History of Rare Solid Tumors protocol for co-enrolled participants (e.g., on samples from responding participants who lack identified abnormalities using the standard panel).

5.2.5 Immunohistochemistry (IHC)

Samples will be assessed for ID3 and ARID1A protein expression. Previous literature reports these molecules are downregulated at the protein level in PACC. In addition, we will assess for RAD51 foci to assess for HRR deficiency in tissue (pre-treatment and end of treatment visit/ time of progression), and for activation of γH2AX in on-treatment (as compared to pre-treatment) samples to determine effect of olaparib. These studies will be performed under the direction of Laboratory of Pathology collaborators Drs. David Kleiner and Stephen Hewitt.

5.2.6 PDX model making

Fresh tissue samples not required for the above analyses will be processed by the Alewine Lab for PDX model development. Coded, linked specimens may be sent to collaborators at Center for Advanced Preclinical Research (NCI Frederick; Serguei Kozlov) for PDX establishment. Established PDX's can be used for future research on PACC including assessment of drug sensitivity. To assess sensitivity to immunotherapy agents, humanized mouse models may be required.

5.3 SAMPLE COLLECTION SCHEDULE

<table>
<tr><th>Test/assay</th><th>Sample type & amount</th><th>Handling/ processing[1]</th><th>Collection point</th><th>Location of specimen analysis[2]</th></tr>
<tr><td>ATAC-seq</td><td rowspan="2">Tissue core</td><td rowspan="2">Fresh or snap-frozen</td><td rowspan="2">Pre-treatment/Baseline; on-treatment (C2 preferred); Progression</td><td rowspan="2">BPC/Arda Lab</td></tr>
<tr><td>Single cell RNA analysis</td></tr>
<tr><td>Cytogenetics</td><td rowspan="2">Tumor tissue (archival or fresh)</td><td rowspan="2">Formalin fixed paraffin</td><td rowspan="2">Pre-treatment/Baseline</td><td>BPC/Reid Lab</td></tr>
<tr><td>Mutation of HR pathway genes</td><td>Laboratory of Pathology (COMPASS)</td></tr>
</table>

Test/assay	Sample type & amount	Handling/ processing[1]	Collection point	Location of specimen analysis[2]
IHC		embedded (FFPE)	Pre-treatment/Baseline; on-treatment (C2 preferred); Progression	Laboratory of Pathology/ Alewine Lab
PDX model	Tumor tissue (fresh only)	Immediate pickup	Pre-treatment/Baseline; On-treatment (C2 preferred); progression	Alewine Lab in collaboration with CAPR Frederick
PBMC storage	PBMC (35 mL)	BD Vacutainer CPT tube syringes	Pre-treatment/Baseline	BPC

1. *Tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator*
2. *The location of specimen analysis may be adjusted at the time the analyses are performed*

5.4 STORAGE, USE, AND SHARING OF SPECIMENS AND DATA FOR SECONDARY RESEARCH

5.4.1 Sample Tracking and Processing

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

5.4.1.1 Biospecimen Processing Core (BPC)

The samples will be placed immediately on wet ice and refrigerated. The date and exact time of each blood draw should be recorded on the sample tube.

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main BPC number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov by e-mail or at 240-858-3191.

5.4.2 Sample Storage and Disposition

Barcoded samples are stored in barcoded boxes according to stability requirements. Access to stored clinical samples is restricted. Unless other permission obtained, identifiable samples are only to be used for research purposes associated with this trial (as per the IRB-approved protocol) by investigators named on the protocol. It is the responsibility of the Principal Investigator to ensure that identifiable samples are being used in a manner consistent with IRB approval.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of a sample tracking database (e.g., Labmatrix). It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor to correlate results with sample characteristics.

5.4.3 Protocol Completion/Secondary Use/Sample Destruction

Any specimens that are remaining at the completion of the protocol will be stored in the conditions described above. The study will remain open so long as sample or data analysis continues. All samples and data from consenting participants will be stored until they are no longer of scientific value or if a participant withdraws consent for their continued use, at which time they will be destroyed.

If at any time the participant withdraws consent from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed or returned to the participant if so requested. The participant's samples and data will be excluded from future distributions, but those which have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

With the permission of the participant, specimens and data collected on this study, identifiable through a code available to the study team, will be stored indefinitely and used for secondary research, including genetic research. Furthermore, the data and/or specimens, may be shared with other investigators in coded (code key not available to recipient) format for secondary research. Any investigator conducting secondary research in human subjects will seek either additional regulatory approval or exemption for research as appropriate.

Data will also be shared in public database per the study's data sharing plan in compliance with NIH policies.

In addition, specimens/data may be anonymized and further research, including genetic research, conducted at the site or other institutions without participant consent. Participants will be informed that the possibility for this type of research exists.

5.5 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.5.1 Description of the scope of genetic/genomic analysis

Identification of specific genetic/epigenetic changes for further analysis will be made by the investigator after taking into account various factors including the prior rate of growth of disease, response to treatment and tumor fraction in the available sample. DNA and RNA will be extracted from normal tissues and tumor samples.

5.5.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

- As part of study efforts to provide confidentiality of participant information, this study will obtain a Certificate of Confidentiality which helps to protect personally identifiable

research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality.

- Tissue and blood samples collected will be coded. DNA, RNA, and protein isolated from these tissues and cell lines and xenografts generated will all be similarly coded. Only personnel involved in this study will have access to both the code and the name of the participant.
- To facilitate genetic research, and for the purpose of publication of research work, data from genomic studies may be deposited in appropriate public databases. Coded data will be deposited in a manner that the participant's identity cannot be traced.

5.5.3 Management of results

Participants will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Participants will be contacted at this time with a request to provide a sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the participant will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling to explain this result. If the participant does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The Principal Investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1, through 30 days following the last dose of the study medication. After 30 days, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study

- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

_X_ Coded, linked data in an NIH-funded or approved public repository.

_X_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

_X_ Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through*:*

_X_ An NIH-funded or approved public repository. Insert name or names: clinicaltrials.gov.

_X_ BTRIS (automatic for activities in the Clinical Center)

_X_ Approved outside collaborators under appropriate individual agreements.

_X_ Publication and/or public presentations.

When will the data be shared?

_X_ Before publication.

_X_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, participants should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

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) guideline

(version 1.1) [32]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- By chest x-ray: ≥20 mm;
- By CT scan:
    - Scan slice thickness 5 mm or under: as ≥10 mm
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be

recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. 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. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. 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.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the

next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. [33-35] In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.[36]

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.3.3 Response Criteria

6.3.3.1 Evaluation of Target Lesions

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

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

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

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

6.3.3.2 Evaluation of Non-Target Lesions

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

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

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

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

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

6.3.3.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

6.3.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.3.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

6.3.6 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of participants with partial response or complete response.

6.3.7 Disease Control Rate

Disease control rate (DCR) is defined as the percentage of participants with partial response, complete response, or stable disease.

6.3.8 Overall Survival

Overall survival (OS) is defined as the length of time from start of treatment until death from any cause.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. 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 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (weekly) when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

All data will be collected in a timely manner and reviewed by the Principal Investigator or a Lead Associate Investigator. Events meeting requirements for expedited reporting as described in Section **7.2.1** will be submitted within the appropriate timelines.

The Principal Investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The Principal Investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 MANUFACTURER PROTOCOL/SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator, it results in any of the following:

- Death,
- A life-threatening adverse event (see Section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon

appropriate 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.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

Pneumonitis has been reported in <1.0% patients treated with olaparib monotherapy in clinical studies. If pneumonitis is confirmed, olaparib treatment should be discontinued and the participant treated appropriately.

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 participant has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

At any time after a participant 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 participants 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 AstraZeneca Patient Safety within the usual timeframe.

Otherwise, after study treatment completion (i.e., including after any scheduled post-treatment follow-up safety 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 participants still being followed up for survival but who have completed the post-treatment follow up period (30 days).

8.1.6.1 Overdose

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

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

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

8.2 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

Reporting will be per the collaborative agreement.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s) and with applicable regulatory requirement(s). This is done through independent verification of study data with source documentation focusing on informed consent process and eligibility confirmation. Further review of drug administration and accountability, adverse events monitoring, and response assessment will occur as documented in a monitoring plan.

This trial will be monitored by CCR quality management staff and/or personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

10.1 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Assess the anti-tumor activity of single agent olaparib a PARP inhibitor, in participants with advanced PACC	Objective response rate (ORR, CR+PR) until 1 year post-last dose of olaparib in the study population.	Determines whether olaparib is an active drug in this patient population. This will be considered a positive study if at least 3 of 13 patients have a response.
Secondary		
Assess the safety of olaparib in advanced PACC	Incidence of treatment-related serious adverse events from start of treatment to 30 days after last treatment as defined by Common Terminology Criteria for Adverse Events (CTCAE) v5.0.	Descriptive endpoint to assess toxicity profile of the study drug in this population.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Assess alternative measures of anti-tumor efficacy such as clinical outcomes and blood biomarkers	Determine disease control rate, median duration of treatment response, median progression-free survival (PFS) and median overall survival (OS) in the study population until 1 year after last olaparib treatment. Identify best response in serum lipase for each treated participant (defined as greatest decrease from baseline measurement during the treatment course).	Descriptive endpoints that may help to determine sample size needed for future Phase 3 study.
Exploratory		
Acquire tumor tissue through research biopsies that can be used to establish new patient-derived xenografts (PDX), cell line and organoid models of PACC	Establishment of at least 3 PDX models of PACC with availability of matched PBMCs collected at baseline, at cycle 2 (preferred) and et the end of treatment.	PDX to be used for future research on PACC including assessment of drug sensitivity. PDX models could be used to derive new cell line and organoid models.
Assess genetic alterations in PACC through genetic mapping techniques and evaluate alterations in HRR and other DNA repair pathways	Describe genetic alterations in PACC anticipated to be important in the DNA repair process by analyzing participant baseline tumor biopsy samples or archival tissue for: • Mutation of HR pathway genes • Tumor cytogenetics changes • Epigenetic changes by ATAC-seq	Seeks to identify factors which make PACC a DNA repair deficient tumor.
Assess alterations in mRNA and protein levels of HRR-related genes such as *BRCA1/2*, *PALB2* and *RAD51*, and functionality of HRR pathway as predictive biomarkers for olaparib	Association of alterations in mRNA and protein levels of HRR-related genes such as BRCA1/2, PALB2 and RAD51, and functionality of HRR pathway with radiologic response to olaparib	Identify biomarkers predictive for response to olaparib
Assess ID3 protein levels and protein levels of DNA repair pathway genes of interest in participant tumor and normal tissue	Percentage of participants with decreased ID3 or DNA damage repair pathway protein levels (such as ARID1A, RAD51, γH2AX) in tumor as compared to adjacent normal pancreatic acinar tissue.	Identify protein level changes that may contribute to a PACC DNA repair deficiency phenotype.
Assess relationship of treatment response to tumor profile	Association of gene mutation profile, copy number variation, and ID3 protein expression with response to olaparib.	Gain a deeper understanding of how PACC responds to olaparib treatment

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	Identify changes in ATAC-seq and scRNA analysis that occur with treatment and determine association with participant treatment response.	

10.2 SAMPLE SIZE DETERMINATION

The objective response rate of BRCA mutant tumors to olaparib monotherapy in the Phase 1 setting in patients with advanced, previously treated disease was found to be 26.2%. Broken down by histology, objective response rates were 31.1% for epithelial ovarian cancer, 12.9% in breast cancer, 21.7% in pancreatic adenocarcinoma, and 50.0% in prostate cancer [29]. If PACC is an HRR deficient tumor responsive to PARP inhibition, then we would expect to see a similar objective response rate in the participant population proposed here. Specifically, we would expect response rate to be most similar to ovarian cancer, another KRAS WT tumor with frequent HRR deficiency.

With 13 participants receiving olaparib, there would be 80% power to rule out a 5% response rate in favor of a response rate consistent with 30%, with a one-sided 0.10 significance level exact binomial test. In practice, if 13 participants receive olaparib and if 2/13 (15.4%) respond, then the lower one-sided 90% confidence bound on 2/13 is 4.2%, which would be marginally consistent with 5%. In addition, the upper one-sided 90% confidence bound on 2/13 is 36%, which demonstrates that 2/13 could be shown to be consistent with a 30% response rate. Alternatively, if 13 participants receive olaparib and if 3/13 (23.1%) respond, then the lower one-sided 90% confidence bound on 3/13 is 8.8%, which exceeds 5%. In addition, the upper one-sided 90% confidence bound on 3/13 is 44%, which demonstrates that 3/13 could be shown to be consistent with a 30% response rate.

It is expected that up to 4 years will be required to enroll up to 13 evaluable participants. Note: With up to 13 evaluable participants required to meet the study endpoints, a small number of participants will be also enrolled to account for possible inevaluable participants (2) – i.e., we intend to initiate study drug in up to 15 participants. To allow for screen failures (5), a total of 20 will be set for the purposes of the NIH accrual ceiling.

10.3 POPULATIONS FOR ANALYSES

Intention to treat any subjects who enroll onto the trial and provide consent and who receive at least one dose of olaparib will be included in the safety evaluation.

10.3.1 Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment with olaparib.

10.3.2 Evaluable for objective response

Participants who have measurable disease present at baseline, have received at least one cycle of therapy (with at least 75% of planned doses administered), and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated in Section **6.3**. (Note: Participants who exhibit objective disease

progression, or tumor or treatment-related death prior to the end of cycle 1 will also be considered evaluable.)

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

The fraction of all evaluable participants who experience a clinical response (CR+PR) will be reported along with a confidence interval. All analyses will be descriptive without formal hypothesis testing performed except as noted.

10.4.2 Analysis of the Primary Endpoint

The fraction of evaluable participants who experience a clinical response from olaparib will be reported along with an 80% and 95% two-sided confidence interval. Participants with clinical progression or death prior to a follow-up scan will be counted as treatment failures. Participants without follow-up radiologic assessment who withdraw from the study due to toxicity will be counted as treatment failures. Those who withdraw from study prior to follow-up radiologic assessment for other reasons may be replaced.

10.4.3 Analysis of the Secondary Endpoints

Disease control rate will be calculated as the fraction of participants with CR + PR +SD (for at least 16 weeks) among all evaluable participants; it will be reported along with a 95% confidence interval.

Duration of response will be reported using the Kaplan-Meier method from the date a response is identified until the date a response ends (by progression or other reason) or the response is continuing, in which case the duration will be censored.

PFS and OS will be determined using the Kaplan-Meier method and will be reported along with a 95% confidence interval for the median of each. PFS will be calculated from the on-study date until the date of progression or death without progression as events, with participants censored if they do not have an event by the date of last known follow-up. OS will be calculated from the on-study date until the date of death; participants who remain alive will be censored at the date last known alive.

Treatment-related changes in serum lipase, a tumor marker in PACC, will be evaluated by determining the difference between best on treatment level of the marker as compared to baseline levels, and tested for statistical significance of the change by a Wilcoxon signed rank test with a two-tailed p-value. If the changes are evaluated at more than one time point, the changes will be evaluated using unadjusted p-values with adjustment for multiple comparisons such as by the Hochberg method.

Analysis of safety is as described in Section **10.4.4**.

10.4.4 Safety Analyses

The fraction of participants who experience a serious toxicity, by grade and type of toxicity, will be reported.

10.4.5 Baseline Descriptive Statistics

Standard baseline demographic characteristics will be reported.

10.4.6 Planned Interim Analyses

None.

10.4.7 Sub-Group Analyses

None.

10.4.8 Tabulation of individual Participant Data

None.

10.4.9 Exploratory Analyses

The exploratory objectives are intended to collect data for use in planning future scientific investigations or clinical research. These analyses are expected to be performed first using descriptive techniques, reporting descriptive statistics including confidence intervals when appropriate. Any statistical tests performed for evaluation of exploratory objectives will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

This study is being conducted under CRADA #02299 with AstraZeneca.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the participant's medical status. Subjects with PACC will be eligible for participation in this study. No clinical treatment studies specific for PACC have previously been reported. As there is no established, evidence-based standard of care for this ultra-rare disease and it is recognized that single agent chemotherapy is ineffective, persons without prior systemic treatment will be permitted to enroll on study if they are unwilling or medically unfit to receive combination chemotherapy regimens that have been case reported as effective for this disease. Persons with large volume ascites, serum albumin < 2.5 mg/dL, or having received paracentesis within the last 4 weeks are excluded from participating in the study as these clinical features are predictive of disease with a life expectancy too short to benefit from olaparib. Persons with HIV must be excluded even if virus is under control because highly-active anti-retroviral therapies required for adequate treatment affect the CYP3A enzyme that is needed for metabolism of olaparib.

Recruitment of participants onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

12.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have PACC, and because of unknown dosing or toxicities of the study agent in the pediatric participant.

12.3 RISK/BENEFIT ASSESSMENT

12.3.1 Known Potential Risks

12.3.1.1 Study drug

Please refer to the risks outlined in the package insert.

12.3.1.2 Study procedures

12.3.1.2.1 Blood sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting. Up to 55 mL of research blood may be collected at any visit but no more than 121.5 ml in an 8-week period.

12.3.1.2.2 Urine collection

No physical risks are associated with urine collection.

12.3.1.2.3 Electrocardiogram

Some skin irritation can occur where the ECG electrodes are placed. The test is completely painless, and generally takes less than a minute to perform.

12.3.1.2.4 Sedation

Biopsies may be done under sedation. Potential side effects of sedation include headache, nausea, and drowsiness. These are generally mild and last no more than a few hours.

12.3.1.2.5 Local anesthesia

Biopsy may be done under local anesthesia. Potential side effects of local anesthesia include drowsiness, headaches, blurred vision, twitching muscles or shivering, continuing numbness, weakness or pins and needles sensation.

12.3.1.2.6 Tumor Biopsy

The risks of the optional research biopsies include pain, bleeding and infection at the biopsy site. In addition, as the biopsies may be collected under CT guidance, subjects in this study may be exposed to radiation as discussed below.

12.3.1.2.7 Imaging

In addition to the radiation risks discussed below, CT scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heart rate and swelling.

12.3.1.3 Risks from Radiation Exposure

On this study, participants may receive up to 4 CT-guided biopsies, and up to 8 CT scans/year. The total radiation dose for research purposes will be approximately 13.6 rem. The risk of getting cancer from the radiation exposure in this study is 1.4% and of getting a fatal cancer is 0.7%.

12.3.1.4 Non-Physical Risks of Genetic Research

12.3.1.4.1 Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Participants will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with participants, family members or health care providers.

12.3.1.4.2 Risk related to possibility that information may be released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the participants, family members or health care providers, this risk will be included in the informed consent document.

12.3.1.4.3 Risk to family or relatives

Family members or relatives may or may not want to be aware of familial tendencies or genetic risks of disease which may cause anxiety about possible future health problems. As previously noted, participants will be notified of any medically significant and actionable incidental findings. Study results will not be shared with participants.

12.3.2 Known Potential Benefits

The potential benefit to a participant that goes onto study is a reduction in the bulk of their tumor which may or may not have favorable impact on symptoms and/or survival.

No clinical trials for PACC have ever been reported and for this reason, there is no standard therapy for this disease currently. Current therapies for advanced PACC typically consist of repurposed regimens used for either pancreatic or colon adenocarcinoma based upon case reports or anecdotal evidence. Clinical responses to single agent chemotherapy are rare and recent studies suggest that the response rate to first-line combination chemotherapy is 30% or less. Recent retrospective case series have reported a median overall survival (OS) in this population of 15-20 months in patients with advanced disease.

Based upon the evidence presented in Section **1.2**, we believe that PACC may represent a subtype of pancreatic cancer that may be uniquely susceptible to PARP inhibitor therapy. This phase 2 study if positive, could offer additional treatment options for participants with this poorly studied and understood disease. Further, the results of this study could help guide the design of future investigations into optimal first line and maintenance regimens for advanced PACC.

12.3.3 Assessment of Potential Risks and Benefits

Olaparib, as studied in the context of treatment of multiple HRR deficient tumors has been generally well tolerated with an acceptable toxicity profile. The risks of hematologic, pulmonary, and embryonic toxicity as described above will be mitigated through frequent laboratory and clinical monitoring as described in Section **3.2** and dose modifications as described in Section **3.3**.

Although the risks of toxicities with olaparib therapy are well described, advanced PACC is an inadequately studied disease with a lack of available therapies in any line of treatment. With median overall survivals of 15-20 months, there is a grave need for novel treatment modalities for this disease and we believe that olaparib is a rational therapy which could potentially provide meaningful responses that could improve participant outcomes.

12.4 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the participant will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic signature) on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the

Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the collaborator(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore,

the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the investigator.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the manufacturer collaborator, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or manufacturer collaborator requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

A determination was submitted to the FDA regarding the use of olaparib used in this study and it was determined that the proposed investigation is IND exempt (IND #160489).

14.1 OLAPARIB

Please see FDA-approved package insert for olaparib for complete agent information.

14.1.1 Source/Acquisition and Accountability

The olaparib tablets used in this study will be supplied under a collaborative agreement with the manufacturer, AstraZeneca. Commercial supply of olaparib will be supplied.

14.1.2 Administration procedures

Please refer to Section **3.2**.

14.1.3 Toxicity

Please see Section **1.2.5**.

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16 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event/Adverse Experience
AFP	Alpha-fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
β-HCG	Beta-Human Chorionic Gonadotropin
BPC	Biospecimen Processing Core
BTRIS	Biomedical Translational Research Information System
BUN	Blood urea nitrogen
CAP	Chest-Abdomen-Pelvis
CAP	College of American Pathologists
CBC	Complete blood count
CC	Clinical Center
CCR	Center for Cancer Research
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
COV	Close-Out Visit
CR	Complete response
CRADA	Cooperative Research and Development Agreement
CrCl	Creatinine clearance
CRF	Case Report Form
CRIS	Clinical research information system
CRP	C reactive protein
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal carcinoma in situ
DCR	Disease control rate
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DSB	Double-strand break
dUCBT	Double umbilical cord blood transplantation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group – performance status
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FISH	Fluorescence in situ hybridization
FFPE	Formalin fixed paraffin embedded

Abbreviation	Definition
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
Hb	Hemoglobin
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HHS	Human and Health Services
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Homologous recombination
HRCT	High Resolution Computed Tomography
HRPP	Human Research Protection Program
HRR	Homologous recombination repair
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IMV	Interim Monitoring Visit
IMP	Investigational medicinal product
INR	International normalized ratio
IOCBP	Individuals of child-bearing potential
IRB	Institutional Review Board
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LP	Laboratory of Pathology
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NCI	National Cancer Institute
NIH	National Institutes of Health
OHSRP	Office for Human Subjects Research Protection
ORR	Objective Response Rate
OS	Overall survival
PACC	Pancreatic Acinar Cell Carcinoma
PARP	Poly-ADP ribose polymerase
PBMC	Peripheral blood mononuclear cell
PD	Progressive Disease
PDX	Patient-derived xenograft

Abbreviation	Definition
PET	Positron Emission Tomography
PHL	Potential Hy's Law
PFS	Progression free survival
PI	Principal Investigator
PR	Partial Response
PT	Prothrombin time
PTT	Partial thromboplastin time
RDW	Red cell distribution width
RECIST	Response Evaluation Criteria in Solid Tumors
QA	Quality Assurance
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SAE	Serious Adverse Event/Serious Adverse Experience
SAV	Site Assessment Visit
SD	Stable Disease
SIV	Site Initiation Visit (SIV)
SOP	Standard Operating Procedure
SSB	Single-strand break
TBL	Total Bilirubin
ULN	Upper limit of normal
VL	Viral load
WBC	White blood cells
WES	Whole exome sequencing
WGS	Whole genome sequencing

17 APPENDICES

17.1 APPENDIX A- PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

17.2 APPENDIX B- ACCEPTABLE BIRTH CONTROL METHODS

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

Women must be postmenopausal or have evidence of non-childbearing status. Postmenopausal is defined as:

- Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments
- Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the postmenopausal 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 sterilisation (bilateral oophorectomy or hysterectomy)

For women of childbearing potential: negative urine or serum pregnancy test within 28 days prior to study treatment and confirmed prior to treatment on Day 1. 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 signing of the informed consent and continue throughout the period of taking study treatment and for at least 6 months after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her study doctor immediately.

Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with olaparib, breastfeeding must be discontinued if the mother is treated with olaparib.

Male participants 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 participants should also use a highly effective form of contraception if they are of childbearing potential (as listed below). Male participants 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 participant 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 6 month after the last dose of study drug for 3 months after last dose *for male participants*. [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 (e.g., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin / EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom

17.3 APPENDIX C- PARTICIPANT OPTIONAL OLAPARIB PILL DIARY

Today's date _____

Participant Name_____ Participant Study ID _____

Cycle #_____ Dosage of tablets dispensed (in mg)_____

INSTRUCTIONS TO THE PARTICIPANT:

1. Complete one form for each cycle (28 days).
2. You will take ___ olaparib tablets twice a day ~**12 hours apart** on every day of the cycle. You must take the tablets with a large glass of water. A light snack (biscuits/ toast) is also recommended to help reduce nausea.
3. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.
4. It is prohibited to consume grapefruit juice while on olaparib therapy
5. If you miss a scheduled dose, you may take the scheduled dose up to 2 hours after the scheduled dose time. If it is more than 2 hours after the scheduled dose time, do not take the missed dose. You should then take the next dose at the scheduled time.
6. Record the date, the number of tablets you took, and when you took them.
7. If you have any comments or notice any side effects, please record them in the Comments column.
8. Please bring your pill bottle and this form to your physician when you go for your next appointment.

DAY	DATE	# Tablets and When Taken	COMMENTS (side effects or missed doses)
1		_____AM _____PM	
2		_____AM _____PM	
3		_____AM _____PM	
4		_____AM _____PM	
5		_____AM _____PM	
6		_____AM _____PM	
7		_____AM _____PM	
8		_____AM _____PM	

9		_____AM _____PM	
10		_____AM _____PM	
11		_____AM _____PM	
12		_____AM _____PM	
13		_____AM _____PM	
14		_____AM _____PM	
15		_____AM _____PM	
16		_____AM _____PM	
17		_____AM _____PM	
18		_____AM _____PM	
19		_____AM _____PM	
20		_____AM _____PM	
21		_____AM _____PM	
22		_____AM _____PM	
23		_____AM _____PM	
24		_____AM _____PM	

25		_____AM _____PM	
26		_____AM _____PM	
27		_____AM _____PM	
28		_____AM _____PM	

17.4 APPENDIX D- MANAGEMENT OF TOXICITY OF OLAPARIB

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. 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 (except following concomitant treatment with CYP3A4 inhibitors – see **Table 4**)

17.4.1 Management of hematological toxicity

Table 5 Management of Hematological Toxicity

Toxicity	Study treatment dose adjustment
CTCAEa gr 1-2	Dose interruption as judged by the investigator; appropriate supportive treatment and causality investigation
Repeat CTCAE gr 1-2	Dose interruption until recovery to CTCAE gr 1 and dose reduction to 250 mg bid as first step and 200 mg bid as second step
Toxicity	**Study treatment dose adjustment**
CTCAE gr 3-4	Dose interruption until recovered to CTCAE gr 1 for max of 4 weeks and dose reduction to **250 mg bid as first step and 200 mg bid as second step**
Repeat CTCAE gr 3-4	Discontinue study treatment **if 2 dose reductions are not able to manage the anemia**

[a] CTCAE Version 4

17.4.1.1 Management of anemia

Participants can enter the study with a haemoglobin value of > 9g/dl, this should be taken into account when considering the management of anemia. Adverse events of anemia CTCAE grade 1 or 2 (Hb > 8 g/dl) should be investigated and managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anemia. 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 participants develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section **17.4.1.3**. However, if a participant develops anemia CTCAE grade 3 (Hb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks. Study treatment can be restarted a**t a reduced dose (see Table 6)** if Hb has recovered to > 9 g/dl. Any subsequently required anemia related interruptions, considered likely to be dose related, or coexistent with newly

developed neutropenia, and or thrombocytopenia, will require **a further** study treatment dose reduction to 200 mg bid.

If a participant has been treated for anemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependent as judged by investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose **if bone marrow recovers.**

Table 6 Management of anemia

Haemoglobin	Action to be taken
Hb < 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 (e.g. 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 (e.g. 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 4 weeks) 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).
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

17.4.1.2 Management of neutropenia, leukopenia, and thrombocytopenia

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a participant 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.

Study treatment can be restarted at the same dose if an adverse event of neutropenia or leukopenia have been recovered up to CTCAE grade 1 (ANC 2 1.5 x 10^9/L).

Any subsequent interruptions will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step (see **Table 7**).

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. If a participant develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a maximum of 4 weeks. In some cases management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines (see **Table 7**).

Table 7 Management of neutropenia, leukopenia and thrombocytopenia

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

17.4.1.3 Management of prolonged hematological toxicities while on study treatment.

If a participant develops prolonged hematological toxicity such as:

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

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

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

17.4.2 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 participant 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.

17.4.2.1 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnoea) 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 Study Physician.

17.4.3 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In clinical trial NCT00753545 (Assessment of efficacy of AZD2281 in platinum-sensitive relapsed serous ovarian cancer), 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 for nausea and within the first 2 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e. 2 pieces of toast or a couple of biscuits). As per international guidance on antiemetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered e.g. dopamine receptor antagonist, antihistamines, dexamethasone.

17.4.4 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible and must be ≤4 weeks to remain on study treatment (see Section **3.2**).

All dose reductions and interruptions (including any missed doses) (see **Table 8**), 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 participant undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

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

Table 8 Dose reductions for study treatment

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

17.4.5 Renal impairment

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

A dose reduction is recommended for participants 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 participants develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

17.5 APPENDIX E- ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

Introduction

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

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

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

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

Definitions

17.5.1 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).

17.5.2 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, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

Identification of potential Hy's Law cases

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

ALT ≥ 3×ULN

AST ≥ 3×ULN

TBL ≥ 2×ULN

When a participant meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (and also to the AstraZeneca representative).

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 central 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 participant meets PHL criteria (see Section **Error! Reference source not found.** for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

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 participant meets PHL criteria (see Section **Error! Reference source not found.** for definition) by reviewing laboratory reports from all previous visits.

Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law criteria not met

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

Inform the AstraZeneca representative that the participant has not met PHL criteria.

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

Potential Hy's Law criteria met

If the participant does meet PHL criteria the Investigator will:

Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Section 8.4 Safety Reporting)

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 participants' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the participant 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. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>
- Complete the three Liver CRF Modules as information becomes available.

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

Review and assessment of potential Hy's Law cases

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

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

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

This section is applicable to participants << 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 participants' 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, then follow the subsequent process described in Appendix B5.

A 'significant' change in the participant'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.

Actions required for repeat episodes of potential Hy's Law

This section is applicable when a participant 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 E6.*

If **No**: Follow the process described in Appendix E4.1.

If **Yes**: Determine if there has been a significant[#] change in the participant'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 E4.

A 'significant' change in the participant'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.