Abbreviated Title: Ph 2 Olaparib in Mesothelioma

CC Protocol #: 18C0097E

Version Date: , February 24, 2020

NCT Number: NCT03531840

Title: Phase II Study of Olaparib in Subjects with Malignant Mesothelioma

NCI Principal Investigator: Raffit Hassan, M.D.
Thoracic and GI Malignancies Branch (TGMB), CCR, NCI
Building 10, Room 4-5330
9000 Rockville Pike
Bethesda, MD 20892
Telephone: 240-760-6232
E-mail: hassanr@mail.nih.gov

Investigational Device:

Device Name:	ClinOmics
IDE Number:	NSR device (as determined by FDA - Q180160)
Holder:	Center for Cancer Research
Manufacturer:	Center for Cancer Research

Commercial Agents: Olaparib

PRÉCIS

Background:

- Malignant mesothelioma is an invasive and often fatal neoplasm that arises from mesothelium that lines several organs.
- Recent studies have identified germline mutations in the gene encoding BRCA1 associated protein-1 (*BAP1*) which can predispose to mesothelioma
- In addition to mesothelioma, germline *BAP1* mutations confer increased susceptibility for the development of several other tumors including uveal melanoma, cutaneous melanoma, renal cell cancers and possibly other cancers
- In addition to *BAP1*, we found several novel germline variants that have previously not been associated with risk of developing mesothelioma.
- As evidenced by recent data derived from ovarian and prostate cancer patients, mutations in DNA repair genes can define subgroups of cancer patients with distinct vulnerabilities to DNA damage response inhibitors.
- Olaparib is a PARP inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated
- Both established and patient derived mesothelioma cell lines with mutated DNA repair genes are sensitive to olaparib.

Objective:

- Determine the efficacy with respect to objective response rate of olaparib in patients with malignant mesothelioma based on somatic or germline mutation status of DNA repair genes

Eligibility:

- Patients must have progressive, histologically or cytologically confirmed malignant mesothelioma.
- Age $\geq$18 years
- Patients must have received prior platinum and pemetrexed based therapies
- Adequate organ and bone marrow function

Design:

- This is a phase II, single center study of olaparib in subjects with malignant mesothelioma
- All subjects will take olaparib by mouth twice daily until disease progression or intolerable side effects
- Subjects will be assessed for safety (continuously) and efficacy (every 6 weeks)
- Subjects will be analyzed in 3 separate comparison groups according to their mutation status
    - Comparison Group 1: Patients with a germline mutation in DNA repair genes
    - Comparison Group 2: Patients with *BAP1* somatic mutations
    - Comparison Group 3: Patients with neither germline mutations nor BAP 1 somatic mutations

- Up to 30 evaluable subjects will be enrolled

TABLE OF CONTENTS

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- Determine the efficacy with respect to objective response rate of olaparib in patients with malignant mesothelioma based on somatic or germline mutation status of DNA repair genes

1.1.2 Secondary Objectives

- To assess the safety and tolerability of olaparib in patients with mesothelioma
- To assess progression free survival in patients with mesothelioma treated with olaparib monotherapy
- To investigate the potential of soluble mesothelin levels and levels of megakaryocyte potentiating factor to predict any therapeutic response

1.2 BACKGROUND AND RATIONALE

1.2.1 Malignant Mesothelioma

Malignant mesothelioma is an invasive and often fatal neoplasm that arises from mesothelium that lines several organs. Common primary sites of origin of mesothelioma are the pleura (80–90%) and peritoneum (10–15%) and rarely the pericardium and tunica vaginalis.[1] Among the three main histologic subtypes of mesothelioma, epithelioid tumors are the most common and have a better prognosis than biphasic and sarcomatoid tumors. Mesothelioma is managed with surgery, usually administered in combination with other modalities of treatment such as chemotherapy or radiation. For patients with unresectable disease, chemotherapy using the regimen of cisplatin plus pemetrexed is the standard of care.[2] The prognosis of patients with unresectable disease is particularly poor with median survival ranging from 10-13 months.

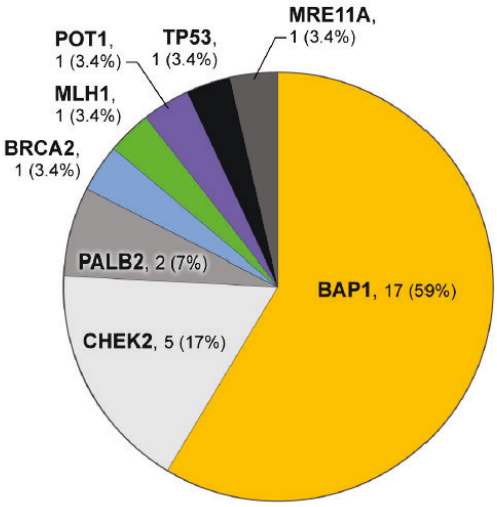


Figure 1: Frequencies of germline mutations in DNA repair genes among 241 consecutive patients with mesothelioma (confidential; unpublished)

Up to 20% of mesothelioma cases occur in patients without significant exposure to asbestos. Risk factors in this cohort are not well understood, but include radiation exposure, exposure to non-asbestos mineral fibers such as erionite, simian virus 40, and genetic predisposition.[1, 3, 4] Recent studies have identified germline mutations in the gene encoding BRCA1 associated protein-1 (*BAP1*) which can predispose to mesothelioma.[3, 4] In addition to mesothelioma, germline *BAP1* mutations confer increased susceptibility for the development of several other

tumors including uveal melanoma, cutaneous melanoma, renal cell cancers and possibly other cancers.

Using germline DNA from 241 consecutive patients enrolled on a prospective study of natural history of mesothelioma, we have found that a deleterious germline mutation is present in 12% of mesothelioma patients (unpublished data, confidential). In addition to *BAP1*, we found several novel germline variants that have previously not been associated with risk of developing mesothelioma. These include mutations in *CHEK2*, *PALB2*, and *BRCA2*, *MLH1*, *POT1*, *TP53, MRE11A*. Figure 1 shows the distribution of germline mutations identified in our cohort.

1.2.2 Preclinical Activity of Olaparib Against Primary Mesothelioma Cell Lines

Olaparib, a poly(ADP-ribose) polymerase inhibitor (PARPi), targets PARP which is required to repair single strand DNA breaks in homologous recombination (HR) repair pathway. Being a first clinically approved PARPi, it exploits synthetic lethality in patients carrying either *BRCA1* or *BRCA2* germline mutations. BRCA 1 associated protein (BAP1) is a deubiquitinase that functions as a tumor suppressor. In HR DNA repair pathway, BAP1 has been shown to interact with BRCA1.

As evidenced by recent data derived from ovarian and prostate cancer patients, mutations in DNA repair genes can define subgroups of cancer patients with distinct vulnerabilities to DNA damage response inhibitors. Our preliminary results also show that established mesothelioma cell lines as well as primary mesothelioma cell lines established from patients with pleural or peritoneal mesothelioma are sensitive to olaparib.

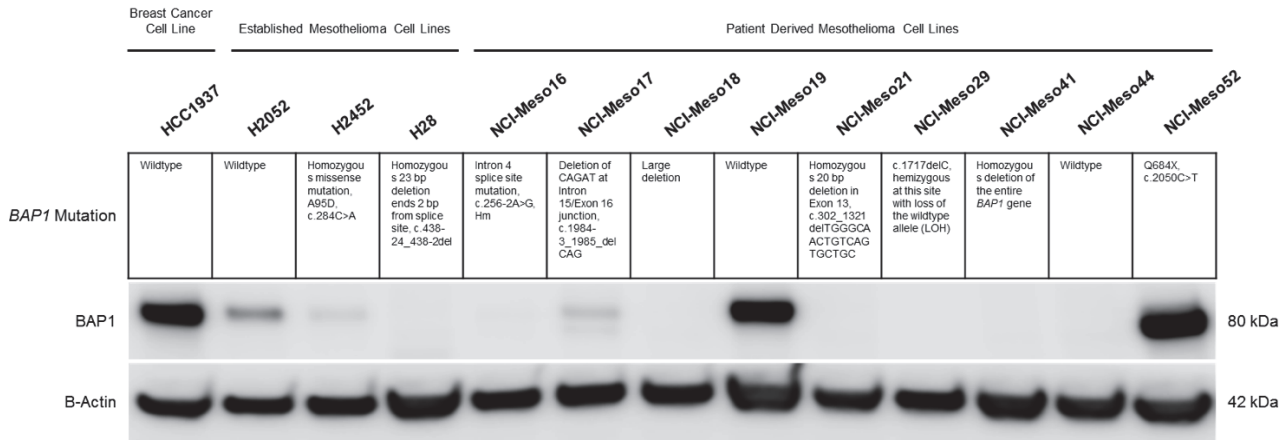


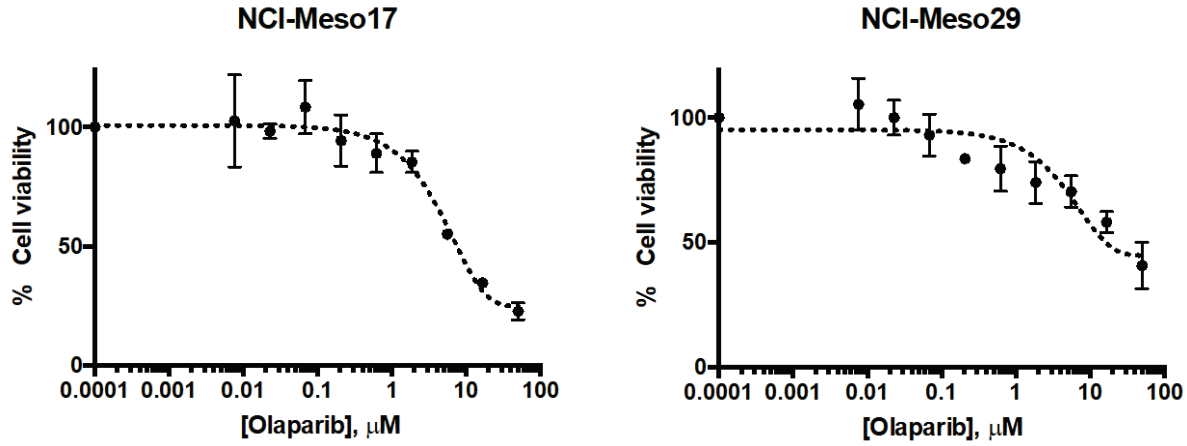
Figure 2. Expression of *BAP1* in different mesothelioma cell lines. Established breast cancer HCC1937 was used as a control cell line that expresses *BAP1* and has been shown to be resistant to olaparib.

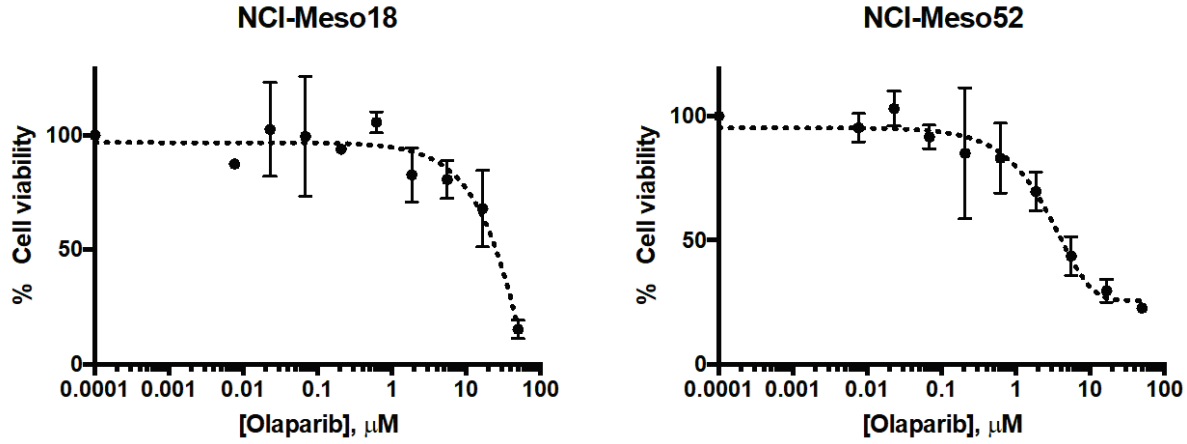
A majority of the mesothelioma cell lines with weak or no *BAP1* expression were sensitive to olaparib (Table 1). However, there are exceptions. For example, NCI-Meso19 and NCI-Meso52 which strongly expressed *BAP1*were equally sensitive to olaparib while as NCI-Meso44 which had no *BAP1* expression was resistant to olaparib. These results suggest that sensitivity of mesothelioma cell lines to olaparib may be dependent on other factors besides *BAP1*. Since the sensitivity of mesothelioma tumors may not be completely dependent on *BAP1* we also plan to enroll patients without *BAP1* mutations on the study. However, the mechanisms that lead to decreased BAP1 protein expression are not well-known.

Table 1. BAP1 expression and sensitivity to olaparib in mesothelioma cell lines.

Cell Line	*BAP1* Expression	Olaparib IC_{50} (μM)
Breast Cancer Cell Line		
HCC1937	Strong	>50
Established Mesothelioma Cell Lines		
H2052	Weak	30
H2452	Weak	40
H28	No	18
Patient Derived Mesothelioma Cell Lines		
NCI-Meso16	No	23
NCI-Meso17	Weak	7
NCI-Meso18	No	24
NCI-Meso19	Strong	24
NCI-Meso21	No	30
NCI-Meso29	No	27
NCI-Meso41	No	31
NCI-Meso44	No	>50
NCI-Meso52	Strong	5

Figure 3*:* Sensitivity of mesothelioma primary cell lines to olaparib.





1.2.3 Olaparib

Olaparib is a PARP inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Olaparib has an established safety profile and it is under investigation in several different cancers.

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

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

BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo[5, 6] and in the clinic.[7] The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair.[8, 9] Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies. Monotherapy with olaparib has shown ORR of about 30% in women with ovarian cancer, with a higher ORR of 40% observed in patients who carried a BRCA mutation.[10] Among patients with HER2-negative metastatic breast cancer and a germline BRCA mutation, olaparib yielded ORR of 60%.[11] Combinations with chemotherapies have shown higher response rates (60-70%) in patients not selected for germline mutations.[12, 13]

PARP inhibitors such as olaparib may also enhance the DNA damaging effects of chemotherapy.[14-16]

1.2.3.1 Pharmacokinetics and drug metabolism in humans

Based on the totality of the efficacy, safety/tolerability profile and the patient convenience of a twice a day dosing schedule, the 300 mg twice daily tablet dose was chosen as the recommended Phase III monotherapy dose (Study D0810C00024).

Following single oral (po) dosing to cancer patients using the tablet formulation, olaparib was rapidly absorbed with peak plasma concentrations typically observed at 1.5 hours. The population PK analysis characterized the absorption phase of olaparib as a sequential zero- and first-order absorption and showed a significant impact of olaparib tablet strength on the absorption rate constant. Following time to maximum plasma concentration (tmax), plasma concentrations of olaparib declined in a biphasic manner with an average terminal elimination half-life (t½) of 14.9 hours (standard deviation [Sd] 8.2 hours).

Following a single 300mg po tablet dose the mean apparent oral plasma clearance was approximately 47.4 L/h (Sd 3.9 L/h). Olaparib exhibited a mean volume of distribution of 158 L (Sd 136 L), indicating distribution into the tissues. The plasma protein binding in vitro was moderate and showed evidence of concentration dependence (81.9% at 10 μg/mL).

1.2.3.2 Clinical Experience

Olaparib monotherapy (tablet formulation) is currently approved in the United States in patients with germline BRCA ovarian cancer and in platinum sensitive ovarian cancer. Investigations are ongoing in patients with gBRCA mutated advanced breast cancer, in patients with gBRCA mutated breast cancer in the adjuvant treatment setting and in patients with gBRCA mutated advanced pancreatic cancer. Additionally, Phase I, II or III studies include investigation of cancers driven by other DNA homologous recombination repair deficiencies beyond BRCA mutations. The approved olaparib monotherapy tablet dose is 300 mg bd.

Olaparib monotherapy is generally well tolerated at monotherapy doses up to 400 mg twice daily (capsule formulation) and 300 mg twice daily (tablet formulation) in patients with solid tumors. AE reports considered to be associated with administration of olaparib are generally mild or moderate (CTCAE Grade 1 or 2) hematological effects (anemia, neutropenia, lymphopenia, thrombocytopenia, MCV elevation), decreased appetite, nausea and vomiting, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache and dizziness.

In a relatively small number of patients, pneumonitis, MDS/AML and new primary malignancies have been reported, however totality of data from the whole development program does not support a conclusion that there is a causal relationship between olaparib and these events. These important potential risks for olaparib are being kept under close surveillance.

1.2.4 Study Rationale

Olaparib, a poly(ADP-ribose) polymerase inhibitor, targets PARP which is required to repair single strand DNA breaks in homologous recombination (HR) pathway. Being a first clinically approved PARPi, it exploits synthetic lethality in patients carrying either *BRCA1* or *BRCA2* germline DNA repair mutations. Using germline DNA from 241 consecutive patients enrolled on a prospective study of natural history of mesothelioma, we have found that a deleterious germline

mutation is present in 12% of mesothelioma patients. In addition to *BAP1*, we found several novel germline variants that have previously not been associated with risk of developing mesothelioma. We hypothesize that a subset of mesothelioma patients with germline or somatic alterations in DNA repair genes could benefit from treatment with PARP inhibitors.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically or cytologically malignant mesothelioma confirmed by the NCI Laboratory of Pathology. Patients with pleural, peritoneal, pericardial or tunica vaginalis mesothelioma are eligible.

2.1.1.2 Archival tumor samples must be available and sufficient for diagnostic and genetic testing; if archival sample insufficient for testing, subject must have lesions amenable to biopsy and be willing to undergo biopsy.

2.1.1.3 Patients must have measurable disease, as defined in sections 6.4.1 and 6.4.2.

2.1.1.4 Patients must have progressive disease at study entry

2.1.1.5 Patients must have received prior platinum and pemetrexed based therapies. Response to platinum is not an eligibility criterion for enrollment.

2.1.1.6 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of olaparib in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

2.1.1.7 ECOG performance status ≤ 1 (see Appendix A).

2.1.1.8 Patients must have a life expectancy of ≥ 16 weeks

2.1.1.9 Patients must have adequate organ and marrow function ≤5days prior to C1D1 as defined below:

leukocytes	≥3,000/mcL
absolute neutrophil count	≥1,500/mcL without growth factor support
platelets	≥100,000/mcL
hemoglobin	≥10 g/dL with no blood transfusion in the past 28 days
total bilirubin	≤1.5 x ULN (unless Gilbert's Disease)
AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal (≤ 5X ULN in the presence of liver metastases)
creatinine clearance	≥ 51 mL/min (calculated using the -Cockcroft-Gault formula.

2.1.1.10 Pre-clinical data indicate that olaparib can have adverse effects on embryofetal survival and development. It is further not known whether olaparib or its metabolites are found in seminal fluid. For these reasons:

2.1.1.10.1 **Women** of childbearing potential and their partners, who are sexually active, must agree to the use of 2 highly effective forms of contraception in combination (male condom plus one of the methods listed in section 2.1.1.10.3) or must totally/truly

abstain from any form of sexual intercourse. This should be started from the signing of the informed consent, throughout their participation in the study and for at least 1 month after the last dose of olaparib.

2.1.1.10.2 **Male patients** must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (see section 2.1.1.10.3) if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

2.1.1.10.3 Acceptable birth control methods:

- Total sexual abstinence i.e., refrain from any form of sexual intercourse in line with the patients' usual and/or preferred lifestyle. Abstinence must be for the total duration of the study treatment and for at least 1month (for female patients) or 3 months (for male patients) after the last dose of study treatment. Periodic abstinence (e.g., calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine Device PLUS male condom. Provided coils are copper-banded.
- Etonogestrel implants (e.g., Implanon®, Norplant®) PLUS male condom
- Normal and low dose combined oral pills PLUS male condom
- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom
- Intrauterine system device (e.g., levonorgestrel-releasing intrauterine system - Mirena®) PLUS male condom
- Norelgestromin/ethinyl estradiol transdermal system PLUS male condom
- Intravaginal device (e.g., ethinyl estradiol and etonogestrel) PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.

2.1.1.11 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any other investigational agents.

2.1.2.2 Patients who have received any previous treatment with a PARP inhibitor, including olaparib.

2.1.2.3 Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment

2.1.2.4 Patients with other malignancy documented as occurring within the last 1 year. 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, or other

solid tumors including lymphomas (without bone marrow involvement) documented as curatively treated or under control for ≥1 year.

2.1.2.5 Patients with features suggestive of MDS/AML on peripheral blood smear.

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

2.1.2.7 History of allergic reactions or hypersensitivity attributed to compounds of similar chemical or biologic composition to olaparib or its excipients.

2.1.2.8 Patients who have had a whole blood transfusion within 120 days prior to enrollment. (Packed red blood cells and platelet transfusions are acceptable, for timing refer to item 2.1.1.9)

2.1.2.9 Patients with persistent toxicities (≥ CTCAE grade 2) with the exception of alopecia, caused by previous cancer therapy

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

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

2.1.2.12 Resting ECG with QTcF > 470 msec on 2 or more time points within a 24-hour period or family history of long QT syndrome

2.1.2.13 Patients that have had major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

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

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

2.1.2.16 Pregnant women are excluded from this study because olaparib has the potential for teratogenic or abortifacient effects. Women must either be post-menopausal or must have a negative pregnancy test (urine or serum) ≤ 28 days prior to enrollment and confirmed on day 1 of cycle 1 of study therapy.

Postmenopausal is defined as:

- Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
- Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50 years of age
- 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)

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

2.1.2.18 Immunocompromised patients are excluded.

2.1.2.19 Patients who are known to be serologically positive for human immunodeficiency virus (HIV). This includes HIV patients on antiretroviral therapy due to the potential for pharmacokinetic interactions with olaparib.

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

2.1.2.21 Previous allogeneic hematopoietic stem cell transplant, allogeneic bone marrow transplant or double umbilical cord blood transplant (duCBT)

2.1.3 Recruitment Strategies

Information about the study will be posted on sites such as clinicaltrials.gov and the CCR recruitment website. In addition, information about this study will be posted on NIH social media platforms. Subjects will also be drawn from patients seen at the mesothelioma clinic at the NIH Clinical Center as well as from referrals from outside providers.

2.2 SCREENING EVALUATION

The following activities will be performed only after the subject has signed the consent for study # 01C0129 on which screening activities will be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

Screening evaluation may be completed within 28 days prior to enrollment unless otherwise noted

- Confirmation of histologic or cytologic diagnosis of mesothelioma by the NCI Laboratory of Pathology. If archival tissue is unavailable or insufficient for this purpose, a fresh biopsy will be collected. This may be performed at any time prior to enrollment. Remaining tissue (fresh or archival) may be used for somatic mutational analysis.
- Medical History including prior cancer therapies, history of blood transfusions
- Physical exam including vital signs and ECOG performance status
- CT scan with contrast of chest, abdomen and/or pelvis and areas of known or suspected disease involvement; MRI may also be performed when appropriate
- FDG-PET scan

- Hematology including blood smear (See footnote in 5 in Study Calendar for detailed list of assessments)
- Biochemistry assessments (See footnote 6 in Study Calendar for detailed list of assessments)
- Coagulation (See footnote 8 in Study Calendar for detailed list of assessments)
- Serum or urine β-hCG in women of childbearing potential (within 28 days prior to enrollment and confirmed on day 1 of cycle 1)
- Urinalysis (See footnote 7 in Study Calendar for additional instructions)
- Electrocardiogram (Performed within 7 days prior to enrollment. See footnote 10 in Study Calendar for additional instructions)

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.3.1 Treatment Assignment and Randomization/Stratification Procedures

Cohorts

Number	Name	Description
1	Mesothelioma	Subjects with malignant mesothelioma

Arms

Number	Name	Description
1	Olaparib	Twice daily oral olaparib

Stratifications

None.

Randomization and Arm Assignment

This is not a randomized study. Subjects 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 subjects with progressive malignant mesothelioma who have previously been treated. Olaparib will be continued until disease progression or unacceptable toxicity. As indicated in section 10, subjects will be analyzed in 3 separate comparison groups according to their mutation status:

- Comparison Group 1: Patients with a germline mutation in DNA repair genes
- Comparison Group 2: Patients with *BAP1* somatic mutations
- Comparison Group 3: Patients with neither germline DNA repair mutations nor *BAP1* somatic mutations

Germline samples for mutation status analysis will be collected and stored in a CLIA certified laboratory Genetics Branch (CLIA# 21D2125203). Tissue (blocks and slides) and fresh biopsies (if collected) will be stored in the NCI Laboratory of Pathology (CLIA#21D0716664). Genetic analysis will be performed retrospectively using the ClinOmics platform.

3.2 DRUG ADMINISTRATION

Olaparib at the dose of 300 mg will be given orally continuously twice daily, with doses taken at the same times each day approximately 12 hours apart. The correct number of 100mg or 150mg tablets comprising the appropriate dose should be taken at the same times each day 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 21-day cycle. Per the CCR policy for self-administered oral investigational agents (PM-8) which will be followed in this protocol, patients will be provided with a pill diary (Appendix C), instructed in its use, and asked to bring it with them to each appointment.

Patients should be given clear instructions on how and when to take their study treatment. Patients 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 section of the eCRF. All patients must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

If a patient misses more than 50% of the doses in any given cycle, the patient will be considered inevaluable for response per sections 10.3.2 and 10.3.3 and will be removed from the study.

Patients 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 of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken, and the patient should take their allotted dose at the next scheduled time. Subjects should avoid grapefruit juice while on study, due to P450 interactions.

3.3 DOSE DELAYS/MODIFICATIONS

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. Study treatment can be modified per Table 2. 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.

Table 2: Dose levels for olaparib dose modification

Dose Level	Olaparib tablets
1 (Starting dose level)	300 mg twice daily
-1	250 mg twice daily
-2	200 mg twice daily

3.3.1 Modifications and Management of Hematologic Toxicities

3.3.1.1 Anemia

Table 3: Dose Delay/Modification and Management of Anemia

Hemoglobin	Action to be taken
Hb < 9 ***but*** **≥ 8 g/dL**	Give appropriate supportive treatment and investigate causality. Investigator judgment to continue olaparib with supportive treatment (e.g. transfusion) *or* interrupt dose for a maximum of 4 weeks. If repeat Hb **< 9** ***but*** **≥ 8 g/dL**, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dL and upon recovery dose reduction to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step may be considered.
Hb < 8 g/dL **(CTCAE Grade 3)**	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks. until improved to Hb ≥ 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.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥ 2-week interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 3.3.1.3 for the management of this.

3.3.1.2 Neutropenia, Leukopenia and Thrombocytopenia

Table 4: Dose Modification and Management of Neutropenia, Leukopenia and Thrombocytopenia

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

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

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours after the last dose of and within 24 hours (14 days for pegylated G-CSF) before resuming study treatment unless absolutely necessary.

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

For cases where patients develop prolonged hematological toxicity (≥ 2-week interruption/delay in study treatment due to CTCAE grade 3 or worse), refer to Section 3.3.1.3.

3.3.1.3 Management of Prolonged Hematological Toxicities while on Study Treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2-week interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTCAE grade 3 or worse neutropenia (ANC < 1000/mcL)
- ≥2-week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50,000/mcL)

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

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

3.3.2 Modifications and Management of Non-Hematologic Toxicities

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

Study treatment can be dose reduced per Table 2. 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.

3.3.2.1 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis.

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

3.3.2.2 Management of nausea and vomiting

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

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

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

3.3.2.3 Renal impairment

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

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 mL/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200mg 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 $\leq$ 30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

3.3.2.4 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible.

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

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

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

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

3.4 STUDY CALENDAR

1 cycle =21 days

Screening assessments must occur within 28 days prior to enrollment unless otherwise indicated. If screening/baseline assessments are performed within 7 days prior to dosing, these assessments do not need to be repeated on C1D1 unless otherwise indicated.

Assessments after and including C1D1 may be performed up to 3 days prior to indicated time unless otherwise indicated.

Dosing cycles after cycle 1 may be delayed for up to two weeks to accommodate schedule conflicts, Federal holidays and inclement weather, etc.

Procedure	Screening[1]	Baseline	Cycle 1		Subsequent Cycles	Treatment discontinuation visit[2]	Post Therapy Follow-up
			Day 1	Day 8	Day 1		
Informed consent	X						
Demographics							
Medical and surgical history	X		X			X	
Prior cancer therapies including radiotherapy	X						
History of blood transfusions[3]	X						
Inclusion exclusion criteria	X						
Physical exam	X		X				
Vital signs	X		X			X	
Performance Score	X		X		X		
Archival or fresh tissue for dx confirmation	X						
Labs[4]							
Full hematology assessment[5]	X		X	X	X	X	
Biochemistry[6]	X		X	X	X	X	

Procedure	Screening[1]	Baseline	Cycle 1		Subsequent Cycles	Treatment discontinuation visit[2]	Post Therapy Follow-up
			Day 1	Day 8	Day 1		
Urinalysis[7]	X		X				
Coagulation[8]	X		X				
Serum or Urine hCG in women of childbearing potential[9]	X		X		X	X	
Electrocardiogram[10]	X		X				
Sample collection for mutational analysis (mandatory)[11]		X					
NIH 527 release form		X[12]					
Correlative Research Studies (See 5.1.2)			X		X	X	
NIH Advance Directives Form[13]		X					
CT CAP (MRI if appropriate); FDG-PET	X		Every 6 weeks ± 7 days			X[14]	X[15]
Adverse Events			X	→	→	X	
Concomitant Medications			X	→	→		

1. Screening evaluations are done within 28 days prior to enrollment with the exception of confirmation of diagnosis (within 6 months prior to enrollment) and ECG (within 7 days prior to enrollment)

2. End of treatment visit will occur approximately 30 days after the last dose of study drug. If the patient is unable to return to the Clinical Center, symptom assessment may be performed via telephone and labs/scans may be performed by an outside provider; the research sample is not required in this circumstance. .

3. Include history of blood transfusion within previous 120 days from start of study treatment and the reasons e.g. bleeding or myelosuppression.

4. These tests will be performed by the NIH CC Department of Laboratory Medicine. Additional analyses may be performed if clinically indicated. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

5. Full hematology assessments for safety: hemoglobin, red blood cells (RBC), platelets, mean cell volume (MCV), mean cell hemoglobin concentration [MCHC], mean cell hemoglobin (MCV), white blood cells (WBC), absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials.

   Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities as defined in Section 3.3.1.3. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted to the manufacturer with an SAE report by the investigator. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.

6. Biochemistry assessments for safety: sodium, potassium, calcium, magnesium, fasting glucose, creatinine, total bilirubin, gamma glutamyltransferase (GGT) – optional on C1D8, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), urea or blood urea nitrogen (BUN), total protein, albumin and lactic dehydrogenase (LDH). In case a subject shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

7. Urinalysis by dipstick should be performed at screening/baseline and then only if clinically indicated. Microscopic analysis should be performed by the NIH Clinical Center Department of Laboratory Medicine if required.

8. Coagulation: activated partial thromboplastin time (APTT) and international normalized ratio (INR) will be performed at screening/baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

9. Two pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. Tests will be performed by the NIH Clinical Center Department of Laboratory Medicine. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

10. ECGs are required within 7 days prior to starting study treatment and when clinically indicated. Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected. ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data

11. Please refer to sections 5.1.2 and 5.3.

12. As indicated in section 5.3.1, patients will be offered the opportunity to identify a designee to receive actionable genetic results. If the patient refuses, this must be documented in the medical record.

13. As indicated in section 12.3, all subjects ≥ age 18 will be offered the opportunity to complete an NIH advance directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

14. Performed only if patient removed from study therapy for reason other than progressive disease

15. Follow up scans will continue every 6 weeks until disease progression. Scans performed outside the NIH Clinical Center are acceptable.

3.5 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit or phone call approximately 30 days following the last dose of study therapy.

3.5.1 Criteria for Removal from Protocol Therapy

- Progressive disease
- Participant requests to be withdrawn from active therapy (see section 3.5.4)
- Requires use of prohibited medication
- Unacceptable Toxicity as defined in section 3.3
- Investigator discretion
- Patient non-compliance
- Positive pregnancy test

3.5.2 Follow Up

By discontinuing from study treatment, the patient is not withdrawing from the study. Patients should be followed for progression (if discontinuation in the absence of progression) as per the Study Calendar.

Any patient discontinuing investigational product should be seen at 30 days post discontinuation for the evaluations outlined in the Study Calendar at the Treatment discontinuation visit. The patient's tumor status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study medication, the principal Investigator/Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the eCRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed as directed in section 6.2.1). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 8.2.1) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study medication to collect and / or complete AE information. For guidance on reporting adverse events to the manufacturer after the 30-day follow up period see Section 8.2.2.

Any patient who has not yet shown objective radiological disease progression at withdrawal from olaparib should continue to be followed as per RECIST as detailed in Study Calendar.

3.5.3 Off-Study Criteria

- Completed study follow-up period
- Patient non-compliance
- Participant requests to be withdrawn from study (see section 3.5.4)

- Death
- Participant lost to follow-up
- The study is discontinued

3.5.4 Withdrawal of Informed Consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- to further participation in the study including any further follow up
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

3.5.5 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

Note: A regularly updated source such the one available here 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 use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the case report form (CRF).

4.1 SUPPORTIVE CARE

Unless otherwise indicated in sections 3.3.1 and 3.3.2, 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 (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), radiotherapy (unless palliative – see 4.5.2), biological therapy or other novel agent) is to be permitted while the patient is receiving study medication. (Note: Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.)

Live virus and live bacterial (including live attenuated) vaccines should not be administered while the patient is receiving study medication and during the 30-day follow up period. An increased

risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

4.3 PERMITTED WITH OLAPARIB DOSING CHANGES

4.3.1 Strong or Moderate CYP3A inhibitors

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

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

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100mg twice daily for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives of the CYP3A inhibitor and any metabolites of the inhibitor that are also CYP3A subfamily enzyme inhibitors.
- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives of the CYP3A inhibitor and any metabolites of the inhibitor that are also CYP3A subfamily enzyme inhibitors.
- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated to the dose that had been or would be administered without concomitant use of an inhibitor.

4.4 PERMITTED WITH CAUTION

4.4.1 Strong or Moderate CYP3A inducers

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

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

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

4.4.2 P-gp Inhibitors

It is possible that co-administration of P-gp inhibitors (e.g. amiodarone, azithromycin) may increase exposure to olaparib. In addition, olaparib is an inhibitor of P-gp. Caution should therefore be observed when olaparib is used concomitantly with substrates, inhibitors, and inducers of P-gp.

4.4.3 Effect of Olaparib on Other Drugs

Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, UGT1A1, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6.

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

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

Examples of substrates include:

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

4.5 PERMITTED MEDICATIONS

4.5.1 Anticoagulant Therapy

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

4.5.2 Palliative Radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

5.1.1 Mesothelin and Megakaryocyte Potentiating Factor (MPF) Serum Samples:

The levels of serum mesothelin as well as megakaryocyte potentiating factor, which is released into serum from the processing of mesothelin precursor protein will be assessed in order to determine correlation with therapeutic response.

5.1.1.1 Sample Collection

Samples will be prior to the first olaparib dose of each cycle and at the end of treatment.

All blood samples will be taken by either direct venipuncture or an indwelling venous access. At each sample collection time, blood (2mL) will be drawn into a 3.5-mL serum separator tube (tiger top tube) labeled as follows:

- Subject ID Number
- Study Number
- Time and date of collection

5.1.1.2 Sample Processing

manner Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

- For sample pickup, page 102-11964.
- For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

Upon arrival in the CPP, each sample should be processed in the following:

Allow blood to clot for 10 minutes and centrifuge to separate the serum within 30 minutes of collection. If unable to process within 30 minutes, then whole blood tubes may be stored upright in refrigerator (4-8°C) for up to 48 hours prior to processing. Processing of samples within 30 minutes is strongly preferred. Stability studies will establish if degradation of soluble mesothelin in whole blood during 0.5 to 48 hours is significant and therefore if the data from these samples should be included in the analysis.

Transfer the serum into two pre-labeled cryotubes and immediately freeze by placing on dry ice. Transfer frozen serum samples into a – 80°C freezer for storage.

5.1.1.3 Sample Storage

All samples will be stored by Dr. Figg's Clinical Pharmacology Program.

5.1.2 Specimen Collection Table

Test/assay	**Volume blood (approx)**	**Type of tube**	**Collection point (+/- 48hrs)**	**Specimen Storage**	**Location of specimen analysis**
MPF and mesothelin	2 mL	3.5 mL serum separator (tiger top)	Day 1 of each cycle (pre-dose) and at end of treatment	(Deliver to Dr. Figg's lab)	Hassan Lab
Mandatory Mutational Analysis	NA	NA	Baseline if tissue (fresh or archival) collected at	Entire collected specimen stored in	Retrospectively analyzed using platform in a

Test/assay	Volume blood (approx)	Type of tube	Collection point (+/- 48hrs)	Specimen Storage	Location of specimen analysis
(Tumor Biopsy) OR			screening is insufficient	the Laboratory of Pathology (Ordered in CRIS)	ClinOmics Core
(Archival Tumor Sample)	NA		Baseline if tissue (fresh or archival) collected at screening is insufficient	Laboratory of Pathology	Retrospectively analyzed in the ClinOmics Core
Mandatory Mutational Analysis (Blood)	8.5 mL	Sodium citrate	Baseline	Molecular Pathology – Deliver blood STAT to building 10/Room 3S245 (open 7:30 AM – 4:30 PM) Ordered in CRIS (indicate for storage only)	Retrospectively analyzed in the ClinOmics Core

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

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.

5.2.1 Blood Processing Core

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts.

Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

5.2.2 NCI Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not placed in paraffin blocks is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled.

5.2.3 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens remaining at the completion of the protocol will be stored in the conditions described above. The study will remain open as long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or until a subject withdraws consent for their continued use, at which time they will be destroyed. Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples, provided they have an IRB-approved protocol and patient consent or an exemption from OHSRP.

The PI will record any loss or unanticipated destruction of samples as a deviation and report to the IRB per the requirements of section 7.2.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

All genetic testing on the protocol will be stored in a CLIA certified laboratory for later analysis using the ClinOmics platform.

A blood sample will be collected and stored for later mandatory germline mutational analysis of DNA repair genes (via whole exome sequencing) as indicated in section 5.1.2.

In addition, leftover tumor tissue from the confirmation of diagnosis may be used for mutational analysis. If insufficient, additional archival tissue may be requested or a fresh tumor biopsy obtained. Collection of tumor biopsy should be guided by ultrasound, CT scan, or other method according to the location of the selected lesion using a ≤ 18-gauge needle to provide cores ideally of at least 20 mm in length or equivalent size. At least 2, ideally 4 core biopsies will be obtained. Fine needle aspiration and biopsy of bone lesions are not acceptable. All biopsies collected under this protocol will undergo review and storage in the NCI Laboratory of Pathology.

All CLIA samples will be stored and tracked by the CLIA laboratories Pathology for tissue (CLIA#21D0716664) and Genetics Branch for blood (CLIA# 21D2125203) according to their detailed CLIA SOP manuals. The research laboratory **must** be bypassed. The freezers are locked, temperature monitored using state of the art equipment according to the CLIA documents. Samples are stripped of identifiers and given an ID according to the CLIA documents. No personal identifiers will be utilized.

Though the intent is to analyze samples as soon as possible, logistical issues may cause delay. Therefore, genetic analysis may be performed on stored blood and tissue samples.

5.3.1 Management of Results

All genetic testing performed on this study will be done in CLIA certified laboratory, the ClinOmics Core though the testing may not be performed in real time.

At the time of consent, subjects will be informed that genetic findings will arise from this study and that information on somatic findings will be provided as well as germline secondary findings. The type of findings to be returned will be discussed as well as the delay in testing.

Participants will be asked complete and sign an NIH-527 Release form at the time of consent. The completion of the form is optional, but a note will be made in the medical record to document refusal. In the event that the participant dies or becomes incapacitated in the time frame between providing a sample for germline analysis and results being available, actionable results will be provided to the individual specified on the release form.

The treating investigator will disclose somatic findings as well as germline findings in which no mutation of clinical utility has been identified to subjects remaining on study at the time the germline analysis is performed.

..

Germline potential clinically actionable findings for the purpose of this study will be flagged as germline mutations that are high confidence pathogenic or likely pathogenic cancer related or American College of Medical Genetics (ACMG) list of genes. The ACMG guidelines for

reporting findings that is current at the time of primary analysis. (A list of current ACMG guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Germline potential clinically actionable variants will be evaluated by the Genetics Branch Genetics Core comprised of a Clinical Geneticist and genetic counsellors. Those deemed to be clinically actionable will be confirmed by COLOR or another CLIA/CAP commercial laboratory from a new DNA sample taken from the patient. Subjects (or designees) will be informed if a clinically actionable gene variant is discovered through a consult with the Genetics Branch who will provide appropriate genetic counseling. The results of the verified actionable germline variant with a consult note will be uploaded into CRIS as part of the medical records.

If the subject or designee 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 secondary 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 an in-house password protected electronic system (C3D) 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. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

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

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section 7.2.1.

6.2 RECORDING OF ADVERSE EVENTS

6.2.1 Time Period for Collection of Adverse Events

Adverse Events will be collected from initiation of study therapy, throughout the treatment period through the 30-day follow up period/treatment continuation visit. Adverse events occurring after the 30-day follow up period will only be recorded if they meet the definition of adverse event of special interest (section8.1.2) or it the adverse event is serious and is deemed related to olaparib.

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.

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 patient's outcome.

6.3 DATA SHARING PLANS

6.3.1 Human Data Sharing Plan

What data will be shared?

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

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
- 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:

- An NIH-funded or approved public repository: clinical trials.gov.
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.3.2 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.

6.4 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 6 weeks (2 cycles). In addition to a baseline scan, confirmatory scans should also be obtained no less than 4 weeks following initial documentation of objective response.

Response and progression will be assessed by the investigator on the basis of physical examinations, computed tomography (CT) or Magnetic Resonance (MR) scans, and potentially other modalities according to standard of care.

For peritoneal mesothelioma, the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[17] will be used. 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.

For pleural mesothelioma, modified RECIST for MPM (malignant pleural mesothelioma)[18] should be used as described in section 6.4.2.

6.4.1 Non-Pleural Mesothelioma

6.4.1.1 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: ≥10 mm
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

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 patient, 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.

6.4.1.2 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 patient 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.[19-21] 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.[22]

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.

6.4.1.3 RECIST version 1.1 Response Criteria

6.4.1.3.1 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.

6.4.1.3.2 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 patient 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).

6.4.1.3.3 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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients 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**

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

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

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

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

Note: Patients 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.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Non-Target Lesions	New Lesions	Overall Response
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.4.2 Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) lesions are difficult to measure reliably.[18] Therefore, modified criteria were defined in 2004 adjusting target lesion measurements to the specific needs of this disease.

6.4.2.1 Modified RECIST Criteria for MPM

Target lesion:

Pleural lesions measurable at baseline and defined as tumor thickness measurements perpendicular to the chest wall or mediastinum in two positions at three separate levels on transverse cuts of CT scan. The sum of those 6 measurements define a pleural unidimensional measure. For reproducibility of lesion identification in follow up scans, cuts were taken at least 1 cm apart and close to anatomical landmarks in the thorax. Reassessments should be done at same position at the same level and by the same reader. Nodal, subcutaneous, and other measurable lesion were measured as per RECIST criteria. All unidimensional measurements were added to obtain total tumor measurement.

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions with no evidence of tumor elsewhere.
- Partial Response (PR): At least a 30% decrease in the total tumor measurement
- Confirmed response (PR and CR): require a repeat scan at least 4 weeks apart
- Progressive Disease (PD): At least a 20% increase in the total tumor measurement, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

6.4.2.2 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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	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	

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

Note: Patients 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.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

6.4.3 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.

6.4.4 Progression-Free Survival

Progression free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Patients that have not progressed or died will be censored at the date of the last tumor assessment.

6.4.5 Objective Response Rate

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

6.4.6 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients with stable disease, partial response or complete response

6.5 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient 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 here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB

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 here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP/IRB in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

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

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at 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 when patients are being actively treated on the trial to discuss each patient.

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 patient 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 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

8.1 Definitions

8.1.1 Adverse Event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs

8.1.2 Adverse Events of Special Interest

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

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

8.1.3 Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening

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

8.2 REPORTING TO ASTRA ZENECA

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

- Include AE cover sheet provided by AstraZeneca and tracking number (ESR-17-12714)
- CC study number
- Patient study number
- Age
- Sex
- Investigational Medical Product (IMP) dose, start & stop date
- SAE onset & stop date
- Event term as reported by the investigator and/or the CTCAE V5 term
- CTCAE grade
- Investigator's assessment of seriousness, according to ICH definitions
- Investigator's assessment of causality
- SAE Outcome
- Date of death, if applicable

Note: The Study tracking number must be provided in the header of the cover note and also in the e-mail Subject. If possible, the study tracking number may also be included in the SAE form.

Reports are sent to:
AEMailboxClinicalTrialTCS@astrazeneca.com or Fax to TCS: 1-302-886-4114)

8.2.1 Serious Adverse Events

If any SAE occurs in the course of the study, then Investigator will inform AstraZeneca within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require

hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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

An AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

8.2.2 Adverse Events after the 30-day follow up period

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

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

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

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

8.2.3 Deaths

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

- Death clearly the result of disease progression should be documented in the DEATH eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within **24 hours** of Investigator

awareness of the event. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.

- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual SAE timeframes (see sections 8.2.1 and 8.2.2).

8.2.4 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.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform AstraZeneca immediately, or **no later than 24 hours** after Investigator awareness of the event.

AstraZeneca will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.2.1. For other overdoses, reporting must occur within 30 days.

8.2.5 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

8.2.5.1 Maternal exposure

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

The outcomes of any conception occurring from the date of the first dose of study medication until 1 month after the last dose of study medication must be followed up and documented.

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

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

AstraZeneca will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.2.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.2.5.2 Paternal Exposure

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

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

The outcome of any conception occurring from the date of the first dose until 3 months *after the last dose* should be followed up and documented.

8.2.6 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

9 IDE HOLDER MONITORING PLAN

As the IDE holder for device trials, FDA regulations require the CCR to maintain a monitoring program. This is done in two parts.

9.1 CLINICAL MONITORING

The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Unanticipated adverse device effect reporting
- Adverse device effect monitoring
- Eligibility confirmation
- Drug administration and accountability
- Response assessment.

The clinical portion of the trial will be monitored by 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

9.2 LABORATORY MONITORING

The program will also include laboratory monitoring for compliance with IDE regulations (§812.46) including device labeling as required under §812.5. Monitors will review data focusing on:

- Informed consent documentation

- Laboratory specimen data related to the collection, processing and storage of biological samples used in the NSR device analysis

The laboratory portion of the trial will be monitored by an NIH contractor for laboratory monitoring. 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 STATISTICAL HYPOTHESIS

The primary objective of this pilot study is to obtain preliminary estimates of the overall response rates to olaparib in patients with malignant mesothelioma according to their individual comparison group:

- Comparison Group 1 - Patients with a germline mutation in DNA repair genes (estimated at 10-12% of all patients);
- Comparison Group 2 - Subjects with *BAP1* somatic mutations (estimated at 50-60% of all patients) and
- Comparison Group 3 - Patients with neither germline DNA repair mutations nor *BAP1* somatic mutations (estimated at 30-40% of all patients).

10.1.1 Primary Endpoint

The primary efficacy endpoints are the objective response rates to olaparib overall, as well as in the three comparison groups of patients. These will be assessed approximately 6 months after enrollment of last subject.

10.1.2 Secondary Endpoints

Secondary objectives include: determining safety and tolerability of olaparib in patients with mesothelioma; estimation of progression free-survival (PFS), identifying biomarkers of response to olaparib, and evaluating serum mesothelin and MPF as biomarkers of anti-tumor efficacy.

Objective	**Endpoints**
Assess safety and tolerability	• Numbers of DLTs identified by type and grade – assessed approximately 21 days after enrollment of last subject.
Assess PFS	• Kaplan Meier analysis of progression free survival in all patients combined – assessed approximately 6 months after enrollment of last subject depending on outcomes noted.
Investigate potential soluble mesothelin levels and MPF	• Comparison of responders vs. non-responders with respect to biomarker baseline level changes over time – assessed approximately 6 months after enrollment of last subject depending on outcomes noted. • Preliminary evaluation of mesothelin and MPF with respect to objective response – assessed approximately 6 months after enrollment of last subject depending on outcomes noted.

Objective	Endpoints
	• Preliminary evaluation of mesothelin and MPF with respect to progression free survival – assessed approximately 6 months after enrollment of last subject depending on outcomes noted.

10.2 Sample Size Determination

The primary objective of this pilot study is to obtain preliminary estimates of the overall response rates to olaparib in patients with malignant mesothelioma according to their individual comparison group:

- Comparison Group 1 - Patients with a germline mutation in DNA repair genes (estimated at 10-12% of all patients)
- Comparison Group 2 - Patients with *BAP1* somatic mutations (estimated at 50-60% of all patients)
- Comparison Group 3 - Patients with neither germline DNA repair mutations nor BAP1 somatic mutations (estimated at 30-40% of all patients).

All patients will be enrolled without consideration of their mutation status, and then the results will be retrospectively categorized and evaluated by mutation type. These results will be used to determine if there are any further patients to be enrolled following an amendment taking into consideration the preliminary results obtained.

It would be desirable if overall there was at least approximately a 20% response rate. The study will initially plan to enroll 30 evaluable patients in order to estimate the overall response rate with a maximum two-sided 90% confidence interval width of +/- 16%. If the observed response rate were 15-20%, the confidence interval width overall would be approximately +/-10-15%. Thus, 30 patients are adequate for an overall assessment of response. If during the initial 20 patients evaluated, there are 0-1 responses noted, then no further patients will be enrolled as soon as this can be determined since the upper one-sided 90% confidence interval bound on 1/20 is 18.1%, which is below the approximate response rate of interest. Because accrual is proceeding rapidly on the study and continued enrollment is desirable at this time, up to 25 total patients may be enrolled (5 additional patients) while awaiting the response evaluations among the first 20 patients.

It is expected that 30 evaluable patients can be enrolled in approximately 12-18 months. As patient non-compliance with study drug dosing will prevent them from being evaluable, the accrual ceiling must be adjusted accordingly. Estimating an average of 3 cycles of study therapy and a non-compliance rate of 10% per cycle the accrual ceiling will be set at 40 patients.

10.3 Populations for Analyses

10.3.1 Evaluable for Toxicity

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

10.3.2 Evaluable for Objective Response, Progression Free Survival and Soluble Mesothelin Levels and PFS

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, have taken at least 50% of the doses per given cycle, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

10.3.3 Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, have taken at least 50% of the doses per given cycle, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.4 Statistical Analyses

10.4.1 General Approach

Response rates will be determined in all patients and in the three comparison groups, based on all evaluable patients, and reported along with appropriate confidence intervals.

10.4.2 Analysis of the Primary Endpoints

After enrollment, when the mutation determination is possible, the response rates will be assessed according to each of the three categories of mutation and the results reported accordingly. The proportions responding in each category will be presented along with 95% confidence intervals. The results obtained will be used to determine if there are any further patients to be enrolled following an amendment taking into consideration the preliminary results obtained.

10.4.3 Analysis of the Secondary Endpoint(s)

The secondary objectives will be assessed using the following measures.

Descriptive tabulations of toxicity will be provided.

Kaplan-Meier analysis of PFS will be performed, including reporting PFS at relevant time points, along with 95% confidence intervals.

Responders vs. non-responders will be compared with respect to serum mesothelin and MPF baseline levels or changes over time (see section 5.1 for biomarkers to be reported), with results compared between response categories using two-tailed Wilcoxon rank sum tests.

Serum mesothelin and MPF at baseline will be categorized into two groups of approximately equal size and tested for their association with PFS using Kaplan-Meier curves and two-tailed log-rank tests. Changes in serum mesothelin and MPF will be determined up until the end of treatment, and landmark analyses will be used to assess their association with PFS.

10.4.4 Safety Analyses

Safety of the agent will be assessed by reporting the grade of adverse events noted in each patient and reporting the proportion with grade 3 and grade 4 adverse events. Safety data will be presented

in individual listings. Summaries will also be prepared. The safety data will consist of the reporting of all adverse events, vital signs, physical examination data, and appropriate laboratory safety data.

10.4.5 Baseline Descriptive Statistics

Limited demographic and clinical characteristics of all patients will be reported.

10.4.6 Planned Interim Analyses

If during the initial 20 patients evaluated, there are 0-1 responses noted, then no further patients will be enrolled as soon as this can be determined. since the upper one-sided 90% confidence interval bound on 1/20 is 18.1%, which is below the approximate response rate of interest. Because accrual is proceeding rapidly on the study and continued enrollment is desirable at this time, up to 25 total patients may be enrolled (5 additional patients) while awaiting the response evaluations among the first 20 patients. .

10.4.7 Sub-Group Analyses

None will be performed.

10.4.8 Tabulation of Individual Participant Data

Toxicity data may be reported on a per-patient basis if adequate events are noted, or may be summarized.

10.4.9 Exploratory Analyses

No exploratory analyses are planned.

11 COLLABORATIVE AGREEMENTS

11.1 Collaborative Research and Development Agreement (CRADA)

The study agent, olaparib, will be provided under a CRADA (# 02299) between NCI and the manufacturer, AstraZeneca.

11.2 Intramural Material Transfer Agreement (iMTA)

Rather than amending the above mentioned CRADA to include the current study, an internal MTA (#43420-27) was executed to make the study agent supplied under the CRADA available for the current study.

11.3 Quality Agreement

As a supplement to address items required by the sponsor that were not addressed in the CRADA or the MTA, a quality agreement was executed between the Raffit Hassan, M.D. and AstraZeneca to establish the obligations and the responsibilities of each party relating to the quality assurance requirements of the manufacture, analysis, packing and/or release by AstraZeneca of products and the supply to the investigator.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale for Subject Selection

This study will be open to all individuals with malignant mesothelioma regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. The selection criteria reflect all available nonclinical and clinical safety experience with olaparib. Further, the selection criteria address the potential pharmacokinetics issues that may confound the reliable assessment of the study objective related to the pharmacokinetic drug-drug interaction.

The treatment of men as well as women is justified because of the severity of the underlying neoplastic disease. Men and women who use appropriate contraception or women who are not of child-bearing potential will be enrolled into this study. The proportion of men and women enrolled into the dose-escalation cohorts of this study depends only on the availability of subjects at the NIH Clinical Center.

12.2 Participation of Children

Children will not participate in this study for the reasons indicated in the eligibility criteria.

12.3 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section 12.4.4), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

12.4 Evaluation of Benefits and Risks/Discomforts

12.4.1 Risks

12.4.1.1 Study Drug

Potential risks of the study include the possible occurrence of any of a range of side effects as listed in section 13.1.3 and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis, provide premedications and supportive therapies as described earlier.

12.4.1.2 Research Blood Collection

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

12.4.2 Image Guided Biopsy Collection

The risks of the research biopsy collected at baseline include pain, bleeding and infection at the biopsy site. In addition, as the biopsy may be collected under CT guidance, subjects in this study may be exposed to approximately 0.80 rem. This amount is below the guideline of 5 rem per year allowed for adult research subjects by the NIH Radiation Safety Committee.

12.4.3 Non-Physical Risks of Genetic Research

These risks are noted in the consent document.

12.4.4 Benefits

The potential benefit to a patient (including those who have lost the capacity to consent) participating in the study is a reduction in the bulk of his/her tumor, which may or may not have a favorable impact on symptoms and/or survival.

12.5 Risk Benefit Assessment

Patients with advanced and/or metastatic mesothelioma, are in continuous need of improved therapy options. This is especially true for patients who have progressed on standard therapy such as the patient population that will be eligible for this trial. Pre-clinical and clinical data (see sections 1.2.2 and 1.2.3) suggest that olaparib may improve outcomes in patients with mesothelioma, particularly in those with mismatch repair defects. A number of clinically appropriate strategies to minimize risk to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines. Overall, the potential benefits of olaparib for mesothelioma patients retaining the ability to consent and those who lose capacity to consent during the course of the trial outweigh the risks associated with the proposed entry-into-human trial with olaparib.

12.6 Consent Process and Documentation

The procedures and tests involved in this study and the associated risks, discomforts and benefits of these processes including the disclosure of genetic results (see section 5.3.1), will be carefully explained to the patient, and a signed informed consent document will be obtained prior to entry onto the study.

12.6.1 Telephone Re-consent

Reconsent by telephone is permitted on this study. Telephone consent will be obtained per OHSRP/IRBO and CCR policies and procedures..

13 PHARMACEUTICAL INFORMATION

There will be no IND obtained for the use of the commercial agent (olaparib) used in this study.

This study meets the criteria for exemption for an IND as this investigation is not intended to support a new indication for use or any other significant change to the labeling; the drug is already approved and marketed and the investigation is not intended to support a significant change in advertising; and the investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

13.1 OLAPARIB)

13.1.1 Source

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

13.1.2 Mode of Action:

Olaparib is an inhibitor of subclasses 1, 2, and 3 of polyadenosine 5' diphosphoribose polymerase (PARP-1, PARP-2, and PARP-3). In tumors that are deficient in the homologous recombination DNA repair pathway (example, BRCA mutants), inhibition of PARP by olaparib causes accumulation of DNA double-strand breaks and genomic instability. Olaparib may also enhance the effects of DNA damage caused by ionizing radiation and chemotherapy.

13.1.3 Toxicity

13.1.3.1 Serious Adverse Events

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

13.1.3.2 Frequent Adverse Events

- Most common adverse reactions and laboratory abnormalities in clinical trials were anemia, nausea, fatigue (including asthenia), vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, nasopharyngitis/pharyngitis/URI, cough, arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash, abdominal pain/discomfort, increase in creatinine, mean corpuscular volume elevation, decrease in hemoglobin, decrease in lymphocytes, decrease in absolute neutrophil count, and decrease in platelets.
- The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 223 patients receiving olaparib: cough, constipation, dysgeusia, peripheral edema, back pain, dizziness, headache, urinary tract infection, dyspnea, and rash.
- The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 223 patients receiving olaparib and not included in the table: leukopenia, stomatitis, peripheral neuropathy, pyrexia, hypomagnesemia, hyperglycemia, anxiety, depression, insomnia, dysuria, urinary incontinence, vulvovaginal disorder, dry skin/ eczema, pruritus, hypertension, venous thrombosis (including pulmonary embolism), and hot flush.

13.1.3.3 Warnings and Precautions

- Myelodysplastic syndrome/Acute Myeloid Leukemia: (MDS/AML) occurred in patients exposed to olaparib, and some cases were fatal. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed.
- Pneumonitis: occurred in patients exposed to olaparib, and some cases were fatal. Interrupt treatment if pneumonitis is suspected. Discontinue if pneumonitis is confirmed.

- Embryo-Fetal toxicity: olaparib can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to avoid pregnancy.

13.1.4 Formulation and preparation

Olaparib tablets are supplied as green, film-coated tablets in 100 mg and 150 mg strengths. The 100 mg strength is also available as a yellow, film-coated tablet.

- 100 mg tablets are 14.5 mm x 7.25 mm oval-shaped
- 150 mg are 14.5 mm x 7.25 mm oval-shaped

Olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain 32 tablets. Olaparib sufficient for 1 21-day cycle + 3 additional days in case of vomiting will be dispensed to patients on Day 1 at the beginning of each subsequent cycle until the patient completes the study, withdraws from the study or closure of the study.

Tablet core components include active drug substance, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black. The yellow tablet film coating only differs from the green film coating with the omission of iron oxide black.

13.1.5 Stability and Storage

All study drugs should be kept in a secure place under appropriate storage conditions. Store in a secure location below 30° C (86° F). Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.

13.1.6 Administration Procedures

Please refer to section 3.2.

13.1.7 Incompatibilities

CYP3A Inhibitors: Avoid concomitant use of strong and moderate CYP3A inhibitors. If the inhibitor cannot be avoided, the dose may be reduced as allowed by protocol.

CYP3A Inducers: Avoid concomitant use of strong and moderate CYP3A inducers. If a moderate CYP3A inducer cannot be avoided, be aware of a potential for decreased efficacy.

13.2 ClinOmics Platform (NSR Device)

13.2.1 Source

The platform was developed in house by the Center for Cancer Research and is available for use by investigators at the NCI. Testing will be performed in the NCI Laboratory of Pathology (CLIA#21D0716664) and/or ClinOmics (CLIA# 21D2125203)

13.2.2 Toxicity

None. However, participants may experience non-physical risks of genetic research as described in section 12.4.3.

14 REFERENCES

1. Robinson BW, Lake RA: **Advances in malignant mesothelioma**. *N Engl J Med* 2005, **353**(15):1591-1603.

2. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C *et al*: **Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma**. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2003, **21**(14):2636-2644.

3. Testa JR, Cheung M, Pei J, Below JE, Tan Y, Sementino E, Cox NJ, Dogan AU, Pass HI, Trusa S *et al*: **Germline BAP1 mutations predispose to malignant mesothelioma**. *Nat Genet* 2011, **43**(10):1022-1025.

4. Bott M, Brevet M, Taylor BS, Shimizu S, Ito T, Wang L, Creaney J, Lake RA, Zakowski MF, Reva B *et al*: **The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma**. *Nat Genet* 2011, **43**(7):668-672.

5. Hay T, Matthews JR, Pietzka L, Lau A, Cranston A, Nygren AO, Douglas-Jones A, Smith GC, Martin NM, O'Connor M *et al*: **Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin**. *Cancer Res* 2009, **69**(9):3850-3855.

6. Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, Derksen PW, de Bruin M, Zevenhoven J, Lau A *et al*: **High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs**. *Proc Natl Acad Sci U S A* 2008, **105**(44):17079-17084.

7. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O'Connor MJ *et al*: **Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers**. *N Engl J Med* 2009, **361**(2):123-134.

8. Helleday T: **The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings**. *Mol Oncol* 2011, **5**(4):387-393.

9. Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, Ji J, Takeda S, Pommier Y: **Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors**. *Cancer Res* 2012, **72**(21):5588-5599.

10. Gelmon KA, Tischkowitz M, Mackay H, Swenerton K, Robidoux A, Tonkin K, Hirte H, Huntsman D, Clemons M, Gilks B *et al*: **Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study**. *Lancet Oncol* 2011, **12**(9):852-861.

11. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, Delaloge S, Li W, Tung N, Armstrong A *et al*: **Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation**. *N Engl J Med* 2017, **377**(6):523-533.

12. Oza AM, Cibula D, Benzaquen AO, Poole C, Mathijssen RH, Sonke GS, Colombo N, Spacek J, Vuylsteke P, Hirte H *et al*: **Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial**. *Lancet Oncol* 2015, **16**(1):87-97.

13. Lee JM, Hays JL, Annunziata CM, Noonan AM, Minasian L, Zujewski JA, Yu M, Gordon N, Ji J, Sissung TM *et al*: **Phase I/Ib study of olaparib and carboplatin in BRCA1 or BRCA2 mutation-associated breast or ovarian cancer with biomarker analyses**. *J Natl Cancer Inst* 2014, **106**(6):dju089.

14. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C *et al*: **Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy**. *Nature* 2005, **434**(7035):917-921.

15. McCabe N, Turner NC, Lord CJ, Kluzek K, Bialkowska A, Swift S, Giavara S, O'Connor MJ, Tutt AN, Zdzienicka MZ *et al*: **Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition**. *Cancer Res* 2006, **66**(16):8109-8115.

16. Menear KA, Adcock C, Alonso FC, Blackburn K, Copsey L, Drzewiecki J, Fundo A, Le Gall A, Gomez S, Javaid H *et al*: **Novel alkoxybenzamide inhibitors of poly(ADP-ribose) polymerase**. *Bioorg Med Chem Lett* 2008, **18**(14):3942-3945.

17. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M *et al*: **New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)**. *European journal of cancer* 2009, **45**(2):228-247.

18. Byrne MJ, Nowak AK: **Modified RECIST criteria for assessment of response in malignant pleural mesothelioma**. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2004, **15**(2):257-260.

19. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, Eisenberger MA, Higano C, Bubley GJ, Dreicer R *et al*: **Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group**. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008, **26**(7):1148-1159.

20. Rustin GJ, Quinn M, Thigpen T, du Bois A, Pujade-Lauraine E, Jakobsen A, Eisenhauer E, Sagae S, Greven K, Vergote I *et al*: **Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer)**. *Journal of the National Cancer Institute* 2004, **96**(6):487-488.

21. Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, Figg WD, Freidlin B, Halabi S, Hudes G *et al*: **Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the**

Prostate-Specific Antigen Working Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1999, **17**(11):3461-3467.

22. Vergote I, Rustin GJ, Eisenhauer EA, Kristensen GB, Pujade-Lauraine E, Parmar MK, Friedlander M, Jakobsen A, Vermorken JB: **Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup**. *Journal of the National Cancer Institute* 2000, **92**(18):1534-1535.

15 APPENDICES

15.1 APPENDIX A – PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

15.2 APPENDIX B -COCKCROFT-GAULT FORMULA

$$\text{Creatine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight in kg}}{(\text{serum creatinine [mg/dL]} \times 72)} \ (\times 0.85 \text{ for females})$$

15.3 APPENDIX C - PARTICIPANT OLAPARIB PILL DIARY

Today's date _____

Patient Name_____ Patient Study ID _____

Cycle #_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle (21 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. You should avoid drinking grapefruit juice while on study.
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. If you miss more than half of the doses (21 tablets) in any cycle, we will have to remove you from the study.
7. Record the date, the number of tablets you took, and when you took them.
8. If you have any comments or notice any side effects, please record them in the Comments column.
9. 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	

DAY	DATE	# Tablets and When Taken	COMMENTS (side effects or missed doses)
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	

DAY	DATE	# Tablets and When Taken	COMMENTS (side effects or missed doses)
20		_____AM _____PM	
21		_____AM _____PM	

Patient's Signature: _____ Date: _____

The Study Team will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study therapy _____
3. Total number of pills taken this cycle (Days 1-21)_____

Physician/Nurse Signature _____

15.4 APPENDIX D – ACTIONS REQUIRED IN CASES OF LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

15.4.1 Introduction

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

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

The Investigator participates 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.

15.4.2 Definitions

15.4.2.1 Potential Hy's Law (PHL)

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

15.4.2.2 Hy's Law (HL)

AST or ALT ≥ 3x ULN together **with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, 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 timeframe within which the elevations in transaminases and TBL must occur.

15.4.3 Identification of Potential Hy's Law Cases

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

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

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

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

15.4.4 Follow-up

15.4.4.1 Potential Hy's Law Criteria not met

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

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

15.4.4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

15.4.4.3 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 Investigator will follow the instructions below.

If there is an 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 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

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

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

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

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

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

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

If Yes:

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

- If there is no significant change no action is required

- If there is a significant change, follow the process described in Section 15.4.4.2 of this Appendix

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