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TITLE: Phase IIA Trial of Delayed Initiation of Olaparib Maintenance Therapy in Platinum Sensitive Recurrent Ovarian Cancer

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Commercial Agent(s): olaparib (Lynparza®, NSC #)

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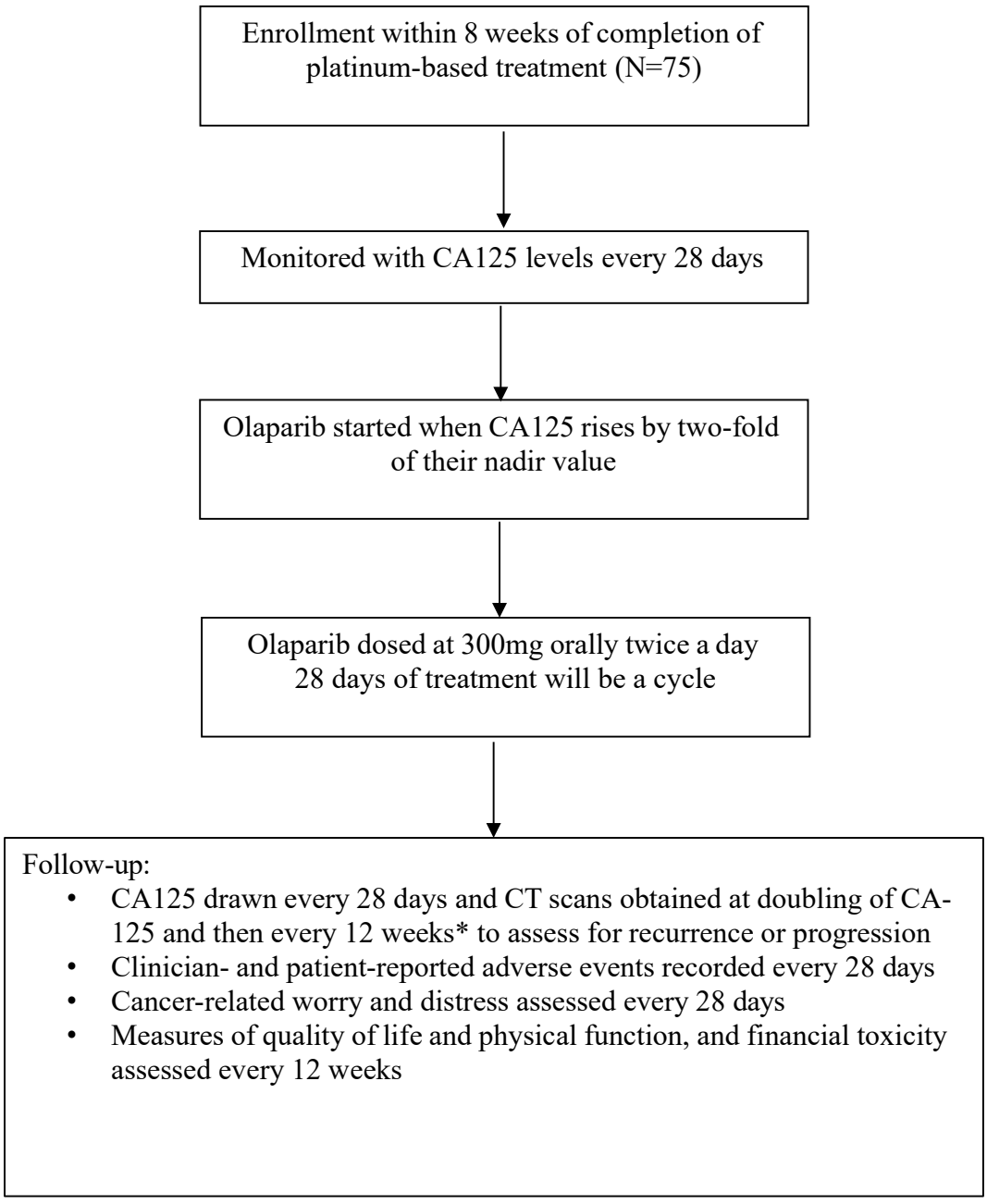
TABLE OF CONTENTS

STUDY SCHEMA



*CT scans can be obtained for rising CA125 or physician preference for patient symptoms

STUDY SYNOPSIS

Title	Phase IIA trial of delayed initiation of olaparib maintenance therapy in platinum sensitive recurrent ovarian cancer
Phase	Phase II
Methodology	Open-label study
Study Duration	42 months
Study Center(s)	Single center, University of Pittsburgh Medical Center
Objectives	**Primary Objective(s):** To estimate the time to next therapy, defined as time from completion of platinum-based therapy for treatment of recurrence until initiation of post-olaparib treatment, for delayed start olaparib in platinum sensitive recurrent epithelial ovarian cancer with a complete or partial response to last platinum therapy . **Secondary Objective(s):** To estimate the progression-free survival (PFS) for delayed start olaparib To estimate the overall survival (OS) for delayed start olaparib To determine the safety and tolerability for delayed start olaparib To determine the overall response rate of delayed start olaparib stratified by BRCA mutational status To evaluate the impact of delayed start olaparib on clinician and patient reported adverse events To evaluate the impact of delayed start olaparib on quality of life To evaluate the impact of delayed start olaparib on physical functioning To evaluate the impact of delayed start olaparib on worry and distress To evaluate the impact of delayed start olaparib on financial toxicity To explore exposure-response relationships between olaparib exposure and toxicity/efficacy **Exploratory Objective:** To evaluate PARP inhibitor resistance mechanisms
Number of Subjects	75 patients

Inclusion Criteria	1. Patient has platinum-sensitive, recurrent ovarian, fallopian-tube or peritoneal cancer. Platinum sensitivity is defined as complete clinical remission after frontline chemotherapy lasting greater than 6 months 2. Patient has completed at least 2 courses of platinum-based chemotherapy and in the most recent course of platinum therapy obtained a PR or CR as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or a CA-125 response, according to Gynecological Cancer InterGroup (GCIG) criteria. 3. BRCA testing required (results not needed for registration) 4. Age ≥18 years old. 5. ECOG performance status score of 0, 1, or 2. See Appendix A 6. Life expectancy greater than 6 months. 7. Normal organ and marrow function as defined below: - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9 /L - Platelets ≥ 100 x 10^9 /L - Hemoglobin (Hgb) ≥ 8 g/dL (blood transfusions to reach this amount are allowed) - Serum creatinine ≤ 1.5 mg/dL - Total serum bilirubin ≤ 1.5 x ULN (in patients with known Gilbert Syndrome, a total bilirubin ≤ 3.0 x ULN, with direct bilirubin ≤ 1.5 x ULN) - AST and ALT ≤ 2.5 x ULN 8. Able to take oral medication. 9. Not pregnant and not breastfeeding. 10. Able to understand and willingness to sign a written informed consent document.
Exclusion Criteria	1. Patient has had a prior invasive malignancy diagnosed within the last five years (except [1] non-melanoma skin cancer or [2] prior in situ carcinoma of the cervix or breast [3] has been without evidence of invasive disease for greater than 3 years) 2. Patients receiving any other investigational agents 3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib 4. Uncontrolled intercurrent illness that could affect their participation in the study including, but not limited to, ongoing or active infection; symptomatic congestive heart failure; unstable angina pectoris; cardiac arrhythmia; known inadequately controlled hypertension; significant pulmonary disease including dyspnea at rest, patients requiring supplemental oxygen, or poor pulmonary reserve; or psychiatric illness/social situations that would limit compliance with study requirements 5. Impairment of gastrointestinal function or disease that may significantly alter the absorption of olaparib 6. Patients who have received prior treatment with a PARP inhibitor 7. History of non-compliance to medical regimens

Study Product(s), Dose, Route, Regimen	Olaparib will be dosed at 300 mg orally twice a day. Twenty-eight days of treatment will be considered one cycle.

Duration of Administration	Patients will be enrolled within 8 weeks of completing platinum-based therapy for recurrent disease. They will be monitored with CA125 levels every 28 days. Olaparib treatment will be started when CA125 rises by two-fold above their nadir value. Patients will continue treatment until disease progression, per RECIST v1.1 or intolerable toxicity, defined as any grade 3 or 4 adverse event, per National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 or the Patient Reported Outcome CTCAE (PRO-CTCAE), that does not resolve completely or return to grade 1 within 28 days after onset.
Reference Therapy	N/A
Statistical Methodology	**Primary endpoint** The time from completion of platinum-based therapy for treatment of recurrence until initiation of post-olaparib treatment **Secondary endpoints** • Progression-free survival (PFS) defined as time from enrollment until detected recurrence or progression of disease, via RECISTv1.1, or death from any cause. • Overall survival (OS) as defined as the time from enrollment to death from any cause. • Toxicity rates defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0 or Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE). • Overall response rate as defined by RECIST or CA-125 and stratified by *BRCA* mutation status. • Patient-reported adverse events using the NCI Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) • Health-related quality of life measured via The Functional Assessment of Cancer Therapy + Ovarian-specific scale (FACT-O) • Physical function assessed through the PROMIS Physical Function-20a assesses self-reported performance of physical activities • Worry and distress measured via Assessment of Survivor Concerns (ASC) Worry Subscale and Impact of Event Scale (IES-R). • Financial toxicity measured through (a) monetary measure using the Modified Collection of Indirect and Nonmedical Direct Costs (COIN), (b) objective measure of financial burden assessed using Barrera et al's Economic Hardship questionnaire, and (c) subjective measure of financial distress will be gauged using the Comprehensive Score for Financial Toxicity (COST Measure) • Exposure as expressed by day 28 trough olaparib concentration measured by LC-MS/MS

1. STUDY OBJECTIVES and ENDPOINTS

1.1. Primary Objective and Endpoint

1.1.1. To determine the time to first subsequent therapy.

1.1.1.1 Endpoint: The time from completion of platinum-based therapy for treatment of recurrence until initiation of post-olaparib treatment, for delayed start olaparib in platinum sensitive recurrent epithelial ovarian cancer with a complete or partial response to last platinum therapy

1.2. Secondary Objectives and Endpoints

1.2.1. To estimate the progression-free survival (PFS) for delayed start olaparib in platinum sensitive recurrent epithelial ovarian cancer with a complete or partial response to last platinum therapy

1.2.1.1. Endpoint: PFS defined as time from enrollment until detected recurrence or progression of disease, via RECISTv1.1, or death from any cause

1.2.2. To estimate the overall survival (OS) for delayed start olaparib in platinum sensitive recurrent epithelial ovarian cancer with a complete or partial response to last platinum therapy

1.2.2.1. Endpoint: OS defined as time from enrollment until death from any cause

1.2.3. To determine the safety and tolerability for delayed start olaparib in platinum sensitive recurrent epithelial ovarian cancer with a complete or partial response to last platinum therapy

1.2.3.1. Endpoint: Toxicity rates defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0

1.2.4. To determine the overall response rate of delayed start olaparib in platinum sensitive recurrent epithelial ovarian cancer with a partial response or complete response to last platinum therapy stratified by BRCA mutational status

1.2.4.1. Endpoint: Overall response rate as defined by RECIST v1.1

1.2.5. To evaluate the impact of delayed start olaparib in platinum sensitive recurrent epithelial ovarian cancer with a complete or partial response to last platinum therapy on patient reported adverse events

1.2.5.1. Endpoint: Patient reported adverse events as reported by the NCI Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE)

1.2.6. To evaluate the impact of delayed start olaparib in platinum sensitive recurrent epithelial ovarian cancer with a complete or partial response to last platinum therapy on quality of life

1.2.6.1. Endpoint: Health-related quality of life measured via The Functional Assessment of Cancer Therapy + Ovarian-specific scale (FACT-O)

1.2.7. To evaluate the impact of delayed start olaparib in platinum sensitive recurrent epithelial ovarian cancer with a complete or partial response to last platinum therapy on physical functioning

1.2.7.1. Endpoint: Physical function assessed through the PROMIS Physical Function-20a assesses self-reported performance of physical activities

1.2.8. To evaluate the impact of delayed start olaparib in platinum sensitive recurrent epithelial ovarian caner with a complete or partial response to last platinum therapy on worry and distress

1.2.8.1. Endpoint: Worry and distress measured via Assessment of Survivor Concerns (ASC) Worry Subscale and Impact of Event Scale (IES-R).

1.2.9. To evaluate the impact of delayed start olaparib in platinum sensitive recurrent epithelial ovarian cancer with a complete or partial response to last platinum therapy on financial toxicity

1.2.9.1. Endpoint: Financial toxicity measured through (a) monetary measure using the Modified Collection of Indirect and Nonmedical Direct Costs (COIN), (b) objective measure of financial burden assessed using Barrera et al's Economic Hardship questionnaire[51], and (c) subjective measure of financial distress will be gauged using the Comprehensive Score for Financial Toxicity (COST Measure).

1.2.10. To explore exposure-response relationships between olaparib exposure and toxicity/efficacy.

1.2.10.1. Endpoint: Exposure as expressed by day 28 trough olaparib concentration measured by LC-MS/MS.

1.3. Exploratory Objective

1.3.1. To evaluate PARP inhibitor resistance mechanisms

1.3.1.1. Characterize genomic changes associated with olaparib resistance: For samples with limited tissue and therefore not amenable to patient derived xenograft (PDX) formation, we will use BROCA analysis on both pre and post-olaparib treatment samples to evaluate genes associated with homologous recombination (HR) defects. For samples for which PDX models are generated, we will perform whole genome sequencing (WGS) on the primary tissue, then compare WGS of primary tumors and PDX tumors. For specific genes in which we find molecular alterations, we will use knockdown and rescue assays in cell lines to validate olaparib resistance related to the identified target.

1.3.1.2. Characterize transcriptome changes associated with olaparib resistance: For an unbiased evaluation of mRNA expression changes associated with olaparib resistance, we will perform RNASeq. RNASeq will be compared between pre and post-olaparib treatment samples. Candidate drivers of resistance will be

compared with BROCA results and then validated with knockin/knockout studies as above.

2. BACKGROUND

2.1. Maintenance Therapy in Ovarian Cancer

Epithelial ovarian cancer (EOC) encompasses cancers that originate in the ovary, fallopian tube and peritoneum, and is diagnosed in ~22,240 women annually in the United States[1]. More strikingly, 14,070 women will die from their disease in 2018, making EOC the 5th leading cause of cancer death in women[1]. Typically diagnosed at an advanced stage, the mainstay of treatment has been cytoreductive surgery followed by adjuvant chemotherapy[2]. Evolving data for the use of neoadjuvant chemotherapy has brought about a gradual practice change, which favors the use of neoadjuvant of chemotherapy for those patients with a low likelihood of primary cytoreduction to less than 1 cm of residual disease, including those with bulky disease and disease in locations not amenable to resection, and/or for patients with a high perioperative risk profile[3]. However, even with this change in practice over the last five years, platinum-containing chemotherapy regimens remain the mainstay of both neoadjuvant and frontline adjuvant therapy for EOC, fallopian tube (FTC) and primary peritoneal cancer (PPC), including after upfront cytoreduction and after interval cytoreduction. This is because these cancers are sensitive to frontline chemotherapy in approximately 75% of women. Unfortunately, most of these women will ultimately experience disease relapse[2]. Those women whose disease returns greater than 6 months after the completion of primary therapy have platinum sensitive disease and are eligible for retreatment with a platinum-based therapy with an increasing response rate based on the amount of time since last treatment. However, there is little chance for a cure.

Because most women with EOC will be in remission at the completion of primary therapy, but eventually experience recurrence, multiple clinical trials have investigated the utility of maintenance therapy in both primary and recurrent setting with the goal of improving survival. While many have shown an improvement in progression-free survival (PFS), none have improved overall survival (OS). Maintenance taxane therapy represents an important cautionary story; Initial results with one year of maintenance taxane therapy (vs. 3 months) showed a 7-month improvement in PFS. This finding led some clinicians to adopt maintenance taxane therapy as a standard of care. However, follow up studies demonstrated no OS advantage for maintenance taxol and significant increases in neuropathy[3-4]. Indeed, a Cochrane database meta-analysis of chemotherapy maintenance trials after frontline therapy were analysed and revealed a combined risk ratio of 1.03 [95% CI 0.96-1.10] for 5-year OS[5].

Improved PFS without improved OS remains a recurring theme for maintenance therapy in EOC. While controversy exists regarding bevacizumab, other anti-angiogenic agents[6-9], pazopanib[10], and nintedanib[11], as well as other targeted agents such as erlotinib[12] have all shown improved PFS without a statistically significant improvement in OS. Other investigators have examined immune targets, interferon-alfa[13], oregovomab[14], and abagovomab[15], and all of the studies conducted, to date, have failed to show a survival advantage.

2.2. Poly ADP-Ribose Polymerase (PARP) inhibitors (PARP-I)

2.2.1 PARP-I Monotherapy

PARP-I were developed as a potential therapy that creates synthetic lethality in cancer cells which

harbor *BRCA* mutations. *BRCA* mutations create homologous recombination (HR) deficiency. HR defective cancer cells are unable to effectively repair double-strand DNA breaks and thus rely on single-strand DNA repair mechanisms. PARP is an instrumental enzyme for single-strand DNA repair via base excision repair (BER). When tumors harbor a *BRCA* mutation and are exposed to a PARP-I the cells can no longer repair DNA with high fidelity via either single- or double-stranded breaks, leading to synthetic lethality. Approximately 15% of women with EOC have a germline *BRCA* pathogenic variant and an additional 10% have a somatic mutation[16-20]. Mutations in other genes in the HR pathway, such as *PALB2, ATM, BRIP1, CHEK2,* and *RAD51* may confer susceptibility to PARP inhibitors increasing the percentage of women with EOC who could potentially benefit from PARP-I treatment by about 20%[21-24]. Initial trials utilizing PARP inhibitors confirmed the concept and effectiveness of synthetic lethality[25-28]. While response rates were higher and more prolonged in *BRCA* mutant tumors, a study of rucaparib in all patients with platinum sensitive EOC showed that the PARP-I was active in ~50% of patients[28].

2.2.2 PARP-I Maintenance Therapy for Recurrent Disease

As PARP-I are more tolerable than chemotherapy for most patients, maintenance therapy studies were soon initiated. Four clinical trials, covering three agents, evaluated the use of PARP-I as maintenance therapy in platinum sensitive disease following either a partial (PR) or complete response (CR) to the most recent platinum-based treatment (Table 1-adapted from Gordon and Temkin)[29-33]. All the trials showed a statistically significant improvement in PFS compared to placebo and led to FDA approval of olaparib, rucaparib, and niraparib as maintenance therapies in recurrent platinum sensitive EOC. These approvals led to widespread practice acceptance for the use of PARP-I. However, despite FDA approval, maintenance therapy remains controversial[33]. This is because, parallel to the experience with other maintenance therapy approaches, to date, none of the PARP-I maintenance trials have demonstrated an OS advantage. Study 19, the only trial to report both PFS and OS data, did not observe an OS advantage for those treated with olaparib; for the entire population, median OS was 29.8-months-[95%-CI-26·9–35·7]-in the olaparib arm vs 27.8 months-[24·9–33·7] in the placebo arm. Additionally, 22% of patients in the olaparib group reported serious adverse events related to nausea, vomiting, fatigue, and anemia[29].

Table 1: Clinical Trials of Maintenance PARP Inhibition in Ovarian Cancer

Study	Study 19	Ariel 3	ENGOT-OV16/NOVA
Agent	Olaparib	Rucaparib	Niraparib
Phase Trial	II (placebo controlled)	III (placebo controlled)	III (placebo controlled)
Number of Patients	265	564	553
BRCA Mutation Status of Patients	Analyzed Retrospectively	Any *BRCA* status	*BRCA* and *non-BRCA* Cohorts Enrolled Independently
Primary Endpoint	PFS	PFS	PFS
Median PFS (PARPI vs Placebo)	8.4 vs 4.8 m	10.8 vs. 5.4 m	21.0 vs 5.5 m (*gBRCA* Cohort) 9.3 vs 3.9 m (*non-gBRCA* Cohort)
OS Data Available	No Statistical Significance	Not Yet Reported	Not Yet Reported
Most Common Grade 3 or 4 AEs	Nausea, Fatigue, Anemia	Anemia, Fatigue, Elevated ALT/AST	Thrombocytopenia, Anemia, Neutropenia
Treatment-Related Deaths	None	Yes, 2 (MDS and AML)	Yes, 1 (AML or MDS)

2.2.3 PARP-I and Financial Toxicity

In addition to traditional measures of toxicity, the risk of financial toxicity in cancer therapy is gaining widespread attention. Financial toxicity is comprised of both objective financial burden of cancer treatment costs (e.g. drug costs, other direct costs, indirect costs from cancer treatment) and subjective financial distress driven by reductions in wealth (income, savings and assets) and cancer-related financial anxiety. Patients with EOC face financial hardships from the costs of initial surgery, multiple lines of therapy, travel for treatment, and lost time at work for patients and their caregivers. In light of the potential for side effects, need for more frequent monitoring, and the cost of treatment, the question then becomes whether or not there is a modification to the current maintenance regimen that could decrease side effects and financial toxicity, while not compromising efficacy.

In September of 2017, the Institute for Clinical and Economic Review examined the effectiveness and value of PARP-I for ovarian cancer[34]. Of the FDA approved PARP inhibitors, olaparib costs $13,679/month. Rucaparib is $13,940/month, and Niraparib costs $14,965/ month. Olaparib maintenance was calculated to be $324,116/ quality-adjusted life year (QALY). Rucaparib maintenance was $369,175/QALY. Niraparib maintenance for those with a germline *BRCA* pathogenic variant was $291,454/QALY and for non-germline pathogenic variant carriers was notably $1,908,822/QALY. While there is no set standard within the US for what an acceptable threshold is, this report uses a value-based benchmark price for a drug defined as the price that would achieve incremental cost-effectiveness ratios of $100,000 and $150,000/ QALY gained. None of these drugs reach this benchmark at their current prices[34].

2.3 **Exploratory Studies Background**

With widespread use of PARP-I, regardless of timing, understanding, and overcoming PARP-I resistance is becoming a major clinical need. BRCA gene reversion[36-37] and mutations in genes in the HR pathway such as RAD51C[38] account for some of the potential etiologies of resistance, but many mechanisms remain unidentified. Evaluating the appropriate timing of PARP-I use represents an important opportunity to collect biospecimens to assess resistance mechanisms and to establish patient-derived xenograft (PDX) tumor models for future therapeutic development.

2.4 **Rationale**

As noted previously, PARP-I have shown efficacy as both monotherapy and as maintenance therapy. For patients with recurrent EOC, a large phase III clinical trial demonstrated that delaying initiation of chemotherapy, as compared to early initiation of chemotherapy, which is considered the current standard of care, not only did not negatively impact patient OS, but also allowed patients to restart treatment 5 months later and reduce overall toxicities. This observation then begs the question as to whether patients with recurrent ovarian cancer could derive the same efficacy benefit from a delayed start of a PARP-I compared to immediate maintenance therapy. Delayed start would have the benefit of sparing the physical, psychological, and financial toxicity associated with prolonged treatment. This approach would be particularly relevant in a population of platinum-sensitive patients who can have prolonged treatment-free intervals. Accordingly, we hypothesize that waiting until the time of chemical recurrence, denoted by rising CA125, to start a PARP inhibitor will lead to an improved time to next therapy with improved quality of life and at a lower financial toxicity. CA-125, which is elevated in greater than 90% of patients with advanced stage ovarian cancer and remains a sensitive marker of recurrent disease, is known to be elevated 3-5 months prior to clinically evident disease. By using this to guide start of olaparib treatment, women can initially remain off of treatment, but also start therapy prior to the start of symptoms associated

with disease, striking a balance between drug toxicity and treatment to alleviate symptom burden from disease. Based on Study 19 data where progression free survival in the placebo arm was 4.8 months and the progression free survival in olaparib treatment arm was 8.4 months, we estimated that by waiting to start olaparib until biochemical relapse will extend time to next treatment by 3 months (8 to 11 months) beyond that reported in the olaparib arm of Study 19.

If this treatment approach is superior or even non-inferior with regard to time to next therapy, it would be an important paradigm shift in the way we use these drugs, leading to similar efficacy outcomes, while decreasing the financial burden and improving overall quality of life. Moreover, by collecting tissue samples before and after treatment and evaluating for resistance mechanisms, PDX models developed from these samples can be used to test for combinations that may reverse the effects of the resistance and/or restore sensitivity to PARP-I, allowing for its use later on in a patient's treatment course.

3. PATIENT SELECTION

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.1. Eligibility Criteria

3.1.1. Patient has platinum-sensitive, recurrent ovarian, fallopian-tube or peritoneal cancer. Platinum sensitivity is defined as complete clinical remission after frontline chemotherapy lasting greater than 6 months

3.1.2. Patient has completed at least 2 courses of platinum-based chemotherapy with a PR or CR as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[39] or a CA-125 response, according to Gynecological Cancer InterGroup (GCIG) criteria[40]

3.1.3. BRCA testing required (results not needed for registration)

3.1.4. Age ≥18 years old

3.1.5. ECOG performance status score of 0, 1, or 2 (See **Appendix A**)

3.1.6. Life expectancy greater than 6 months

3.1.7. Normal organ and marrow function as defined below:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelets ≥ 100 x 10^9/L
- Hemoglobin (Hgb) ≥ 8 g/dL (blood transfusions to reach this amount are allowed)

- Serum creatinine ≤ 1.5 mg/dL
- Total serum bilirubin ≤ 1.5 x ULN
-AST and ALT ≤ 2.5 x ULN

3.1.8. Able to take oral medication

3.1.9. Not pregnant and not breastfeeding

3.1.10. Able to understand and willingness to sign a written informed consent document

3.1.11. Patients must be enrolled within 8 weeks of completing last cycle of chemotherapy

3.2 Exclusion Criteria

3.2.1 Patient has had a prior invasive malignancy diagnosed within the last five years (except [1] non-melanoma skin cancer or [2] prior in situ carcinoma of the cervix or breast [3] has been without evidence of invasive disease for greater than 3 years)

3.2.2 Patients receiving any other investigational agents

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

3.2.4 Uncontrolled intercurrent illness that could affect their participation in the study including, but not limited to, ongoing or active infection; symptomatic congestive heart failure; unstable angina pectoris; cardiac arrhythmia; known inadequately controlled hypertension; significant pulmonary disease including dyspnea at rest, patients requiring supplemental oxygen, or poor pulmonary reserve; or psychiatric illness/social situations that would limit compliance with study requirements

3.2.5 Impairment of gastrointestinal function or disease that may significantly alter the absorption of olaparib

3.2.6 Patients who have received prior treatment with a PARP inhibitor

3.2.7 History of noncompliance to medical regimens

3.3 Inclusion of Women and Minorities

This clinical trial will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients in this protocol to address the study objectives in a population representative of the entire ovarian cancer population. (See Planned Enrollment Table in Section 13.2)

4. SUBJECT SCREENING AND REGISTRATION PROCEDURES

Subjects will be identified in the outpatient clinic. After informed consent is obtained, all patients satisfying the inclusion/exclusion criteria must have eligibility confirmed by the Clinical Trials

Office. The patient will not be considered registered and enrolled in the study until all information is confirmed by the Clinical Trials Office of Research Staff. To enroll a patient, contact the Gyn/Onc Research group Monday through Friday, 8:00AM-4:00PM.

5. SURVEILLANCE MONITORING PLAN

This is a single-arm, open-label phase II clinical trial evaluating delayed start olaparib maintenance therapy, based on a rise in CA125, for patients with epithelial ovarian cancer who have had a partial or complete response to platinum-based treatment. Patients will be enrolled within 8 weeks of completing platinum-based therapy for recurrent disease. At the time of enrollment, patients will be monitored with CA125 levels every 28 days.

At the first evidence of a two-fold rise in CA125 from baseline, patients will undergo a CT scan to evaluate for any visible lesions, including new lesions for those with CR and new, persistent or progressive lesions for those with PR to most recent therapy, and then will be started on olaparib therapy. In the setting of new or progressive lesions, patients will be followed per protocol. Patients may undergo CT imaging prior to rise in CA-125 at the discretion of the treating physician for patient symptoms. Eighty-one patients will be enrolled through UPMC medical and gynecologic oncology offices.

6. TREATMENT PLAN

As noted above, at first evidence of two-fold rise in CA125, patients will undergo a CT scan to evaluate for any visible lesions and then will be started on olaparib therapy.

The trial will involve the optional collection of tumor samples at enrollment (archival tissue) and at the time of recurrence or progression, if biopsies are obtained as part of standard of care, to understand the PARP-I resistance mechanisms.

6.1. Agent Administration

Olaparib treatment will be started when CA125 rises by two-fold of their nadir value. Olaparib will be dosed at 300 mg orally twice a day. Twenty-eight days of treatment will be considered one cycle. Patients will be required to maintain a medication diary (**See Appendix B**).

Patients starting olaparib will continue treatment until disease progression, per RECIST v1.1[39] or intolerable toxicity, defined as any grade 3 or 4 adverse event, per National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0 or Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE), that does not resolve completely or to grade 1 within 28 days after onset. Patients removed from study for unacceptable adverse event(s) will be followed closely until resolution or stabilization of the adverse event (at least 30 days).

Olaparib is FDA-approved for maintenance therapy for patients with platinum sensitive recurrent epithelial ovarian cancer with a complete or partial response to most recent platinum based chemotherapy. Therefore, drug will be covered by standard insurance. Additionally, after discussion with The UPMC Health Plan, they will approve treatment after 2 prior lines even with the delay in standard start time defined by the maintenance indication.

Treatment will be administered on an outpatient basis. Appropriate dose modifications are described in Section 7. No other investigational or commercial agents or therapies may be administered with the intent to treat the patient's malignancy.

Reported adverse events and potential risks are described in Section 7.

6.2. General Concomitant Medication and Supportive Care Guidelines

6.2.1. Concomitant Therapy:

Patients must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days of starting study treatment through the 30-day safety follow up visit should be reported on the Case Report Form. If concomitant therapy must be added or changed, the reason and name of the drug/therapy will be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics +/- steroids), with the following exceptions:

- No other investigational therapy will be given to patients.
- No anticancer agents other than the study medication administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Leukocyte growth factors (e.g., G-CSF and GM-CSF) are not to be administered systematically but may be prescribed by the investigator for severe neutropenia if this is thought to be appropriate.
- No live vaccines will be administered to patient due to immunosuppressant potential of olaparib.

Drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A should be avoided in association with olaparib as these can alter drug metabolism. Strong inhibitors or inducers of the isoenzyme CYP3A should not be administered as systemic therapy and should be avoided whenever possible (See Appendix C). Investigators should consult a frequently updated drug information reference for a list of strong inducers and inhibitors.

- ***CYP3A inhibitors:*** Avoid concomitant use with moderate or strong CYP3A inhibitors (consider alternative agents with less CYP3A inhibition). If co-administration with a **moderate** CYP3A inhibitor cannot be avoided, reduce dose to 150 mg twice daily. If co-administration with a **strong** CYP3A inhibitor cannot be avoided, reduce dose to 100 mg twice daily.
- ***CYP3A inducers:*** Avoid concomitant use with moderate or strong CYP3A4 inducers; a potential for reduced olaparib efficacy exists if moderate CYP3A inducers cannot be avoided.

6.2.2. Supportive care

No routine prophylactic medications are indicated at the start of therapy. In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed with the exceptions noted in 6.2.1

6.3. Duration of Therapy

Patients will be enrolled continuously to the study. Patients will continue evaluation and treatment until one of the following criteria applies:

- Disease progression per RECIST v1.1[39]
- Unacceptable adverse event(s) defined as any grade 3 or 4 adverse event, per National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0 or PRO-CTCAE, that does not resolve to grade $\leq$ 1 within 28 days after onset.
    - Treatment will be interrupted for any grade 3 or 4 event related to treatment. If the toxicity resolves entirely or to grade 1, treatment will be restarted with a dose reduction. If the event does not resolve within 4 weeks or if two previous treatment interruptions with subsequent dose reductions occur, the patient will be withdrawn.
- Patient withdraws consent.
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study.
- Intercurrent illness that prevents further administration of treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.4. Duration of Follow Up

Patients will be followed until the initiation of the next therapy post olaparib treatment. Each patient, regardless of reason for removal from study, will have at least 18 months follow up relative to time of enrollment. Secondary efficacy endpoints will be tracked after official follow-up has been completed.

Assessments in follow up:

- Office visit or review of medical records every 3 months
- Survival endpoints both progression free survival (PFS) and overall survival (OS)

6.5. Criteria for Removal from Study

Patients will be removed from treatment when any of the criteria listed in Section 6.3 apply or once they have completed follow-up as described in Section 6.4. The reasons for treatment discontinuation and study removal and the associated dates must be documented in the Case Report Form.

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

- Patient withdraws consent (termination of treatment and follow-up);
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
- Patient is unable to comply with protocol requirements;

- Treating physician judges continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- Lost to follow-up: if a research subject cannot be located to document PFS after 6 months, the subject will be considered "lost to follow up"
- Termination of the study by the University of Pittsburgh Medical Center
- Patient completes protocol treatment and follow-up criteria.

6.6. **Duration of Study**

Patients are considered on study from the date of enrollment until initiation of post-olaparib therapy or for 30 days after removal from trial for any adverse event to allow for safety monitoring. Secondary efficacy endpoints will be tracked.

7. DOSING DELAYS/DOSE MODIFICATIONS

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5, and the NCI Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE).

7.1. Hematologic Toxicity

Toxicity/Grade	**Dose Adjustment and Management Recommendations**
Anemia (Hemoglobin)	
Grade 1 (≥10.0 – LLN g/dL)	No dose adjustment required.
Grade 2 (≥8.0 – <10.0 g/dL)	No dose adjustment required.
Grade 3 (<8.0 g/dL)	Dose interruption until recovery to grade ≤1. Monitor hemoglobin weekly until recovery. If resolves to grade ≤1 within 28 days, resume at reduced dose 250 mg PO BID. Dose may be reduced to 200 mg PO BID if recurs at reduced dose, but if recurs for a third time, treatment should be discontinued.
Grade 4 Life-threatening consequences; urgent intervention indicated	Dose interruption until recovery to grade ≤1. Monitor hemoglobin weekly until recovery. If resolves to grade ≤1 within 28 days, resume at reduced dose 250 mg PO BID. Dose may be reduced to 200 mg PO BID if recurs at reduced dose, but if recurs for a third time, treatment should be discontinued.
Thrombocytopenia	
Grade 1 (≥75 x 10^9/L)	No dose adjustment required.
Grade 2 (≥50 x 10^9/L – <75 x 10^9/L)	Dose interruption until recovery to grade ≤1. Monitor platelets weekly until recovery. If resolves to grade ≤1 within 28 days, resume at reduced dose 250 mg PO BID.

	Dose may be reduced to 200 mg PO BID if recurs at reduced dose, but if recurs for a third time, treatment should be discontinued.
Grade 3 (≥25 x 10^9/L - <50 x 10^9/L)	Dose interruption until recovery to grade ≤1. Monitor platelets weekly until recovery. If resolves to grade ≤1 within 28 days, resume at reduced dose 250 mg PO BID. Dose may be reduced to 200 mg PO BID if recurs at reduced dose, but if recurs for a third time, treatment should be discontinued.
Grade 4 (<25 x 10^9/L)	Dose interruption until recovery to grade ≤1 Monitor platelets weekly until recovery. If resolves to grade ≤1 within 28 days, resume at reduced dose 250 mg PO BID. Dose may be reduced to 200 mg PO BID if recurs at reduced dose, but if recurs for a third time, treatment should be discontinued.
Absolute neutrophil count (ANC)	
Grade 1 (≥1.5 x 10^9/L)	No dose adjustment required.
Grade 2 (≥1.0 - <1.5 x 10^9/L)	No dose adjustment required.
Grade 3 (≥0.5 - <1.0 x 10^9/L)	Dose interruption until recovery to ≥1.0 x 10^9/L. If resolves to grade ≤1 within 28 days, resume at reduced dose 250 mg PO BID. Dose may be reduced to 200 mg PO BID if recurs at reduced dose, but if recurs for a third time, treatment should be discontinued.
Grade 4 (<0.5 x 10^9/L)	Dose interruption until recovery to ≥1.0 x 10^9/L. Re-initiate olaparib at 250 mg PO BID. If toxicity recurs at grade 4: temporary dose interruption until recovery to ≥1.0 x 10^9/L and r
Febrile neutropenia	
Grade 3 ANC <1.0 x 10^9/L with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than one hour	Dose interruption until improvement of ANC ≥1.0 x 10^9/L and no fever. Restart with dose reduction of 250 mg PO BID. If febrile neutropenia recurs, discontinue olaparib.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue olaparib

Treatment-related anemia may be managed by transfusions without interruption of treatment
Any hematologic AE that does not resolve to grade ≤1 within 28 days despite maximum supportive care remove from study.
For severe hematologic toxicity or in cases where blood transfusion is still required despite dose reductions, interrupt olaparib and initiate appropriate hematologic investigation. If blood parameters remain clinically abnormal after 4 weeks of dose interruption, bone marrow biopsy and cytogenetic analysis should be considered.

7.2. Non-Hematologic Toxicity Attributable to Olaparib

General Olaparib Dose Adjustment and Management Recommendation of Non-Hematologic Toxicity

Grade	Dose Adjustment and Management Recommendations

1	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.
2	Initiate appropriate medical therapy and monitor. If symptoms do not resolve or worsen while on medical therapy, dose interruption until recovery to grade ≤1. Re-initiate olaparib at the same dose. • If the same toxicity recurs at grade 2, interrupt olaparib until recovery to grade ≤1. Re-initiate olaparib at the next lower dose. (250 mg PO BID).
3	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate olaparib at the next lower dose level. • If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤1 and reduce olaparib dose the next lower dose level. (250 mg PO BID). • If toxicity recurs at grade 3, discontinue olaparib.
4	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate olaparib at the next lower dose level. • If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤1 and reduce olaparib dose the next lower dose level. (250 mg PO BID). • If toxicity recurs at grade 4, discontinue olaparib.

7.2.1. **Nausea/vomiting**

Prompt treatment of mild/moderate nausea/vomiting with antiemetics.
If not controlled with medication, interrupt olaparib treatment; when symptoms are grade 1, restart olaparib treatment per protocol.

7.2.2. Fatigue

Evaluate for other possible causes of fatigue (eg anemia, insomnia, depression, hypothyroidism).
Supportive care to cope with fatigue (e.g. strategies to conserve energy, scheduled nap, and exercise).
If not controlled with supportive care, interrupt olaparib treatment; when symptoms are grade 1, restart olaparib treatment per protocol.

7.2.3. Dysgeusia

Supportive care to cope with dysgeusia (appropriate expectation counseling, modification food preparation).
If not controlled with supportive care, interrupt olaparib treatment; when symptoms are grade 1, restart olaparib per protocol.

7.2.4. Diarrhea

Evaluate for other possible causes (eg infection, dietary, concomitant medications).
If other sources are ruled out, initiate anti-motility agents for mild to moderate symptoms.

If not controlled with medication, interrupt olaparib treatment; when symptoms are grade 1, restart olaparib treatment per protocol.

7.2.5. Constipation

Evaluate for other possible causes (eg bowel obstruction, dietary, concomitant medications).
If other sources are ruled out, initiate stool softeners and/or laxatives for mild to moderate symptoms.
If not controlled with medication, interrupt olaparib treatment; when symptoms are grade 1, restart olaparib treatment per protocol.

7.2.6. Pneumonitis

Interrupt olaparib and investigate patients with new or worsening respiratory symptoms, such as dyspnea, cough and fever, or a radiological abnormality consistent with pneumonitis.
If pneumonitis confirmed, discontinue olaparib and treat appropriately (glucocorticoids).

7.2.7. Renal Impairment

CrCl 51 to 80 mL/minute: No dosage adjustment necessary; monitor closely for toxicity, as an increase in mean AUC has been observed in patients with mild impairment.

CrCl 31 to 50 mL/minute: Reduce dose to 200 mg twice daily.

CrCl ≤30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

7.2.8. Hepatic Impairment

Child-Pugh classification A or B: No dose adjustment.

Child-Pugh classification C: Use not recommended for use as safety and pharmacokinetics have not been studied in these patients.

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. For this trial, routine and expedited reporting will begin at the start of study therapy. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

8.1. Adverse Events and Potential Risks List for Olaparib

>10%:

Cardiovascular: peripheral edema (14%)

Central nervous system: fatigue (≤67%), headache (15% to 26%), dizziness (7% to 20%)

Endocrine & metabolic: hypomagnesemia (5% to 14%)

Gastrointestinal: nausea (58% to 77%), abdominal pain (45%), vomiting (30% to 43%), diarrhea (21% to 37%), constipation (16% to 28%), dysgeusia (9% to 27%), dyspepsia (8% to 25%), decreased appetite (16% to 22%), stomatitis (4% to 20%; grades 3/4: 1%)

Genitourinary: urinary tract infection (13% to 14%)

Hematologic & oncologic: increased MCV (57% to 89%), decrease in absolute neutrophil count (25% to 51%; grades 3/4: 7% to 11%), anemia (23% to 44%; grades 3/4: 7% to 21%), neutropenia (5% to 27%; grades 3/4: 6% to 9%), leukopenia (2% to 25%; grades 3/4: 3% to 5%), thrombocytopenia (4% to 14%; grades 3/4: 1%)

Infection: influenza (≤36%)

Neuromuscular & skeletal: asthenia (≤66%), arthralgia (≤30%), myalgia (≤30%), musculoskeletal pain (≤21%), back pain (14%)

Renal: increased serum creatinine (3% to 45%)

Respiratory: nasopharyngitis (≤36%), respiratory tract infection (≤36%), rhinitis (≤36%), sinusitis (≤36%), bronchitis (≤28%), cough (16% to 18%), dyspnea (13% to 15%)

1% to 10%:

Cardiovascular: edema (8% to 9%), pulmonary embolism (≤1%), venous thrombosis (≤1%)

Central nervous system: peripheral neuropathy (5%), depression, insomnia

Dermatologic: skin rash (5% to 6%), dermatitis (1%)

Gastrointestinal: upper abdominal pain (7%)

Hematologic & oncologic: lymphocytopenia (1% to 8%), myelodysplastic syndrome (acute myeloid leukemia; 1%)

Hypersensitivity: hypersensitivity reaction (2%)

Miscellaneous: fever (8% to 10%)

<1%, postmarketing, and/or case reports: pneumonitis

8.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

8.3 Expedited Adverse Event Reporting

8.3.1 Expedited Reporting Guidelines

Use the protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

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

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

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

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

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

8.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial.

8.5 Secondary Malignancy

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

All secondary malignancies that occur following treatment with the trial agent should be reported expeditiously. Three options are available to describe the event:

8.5.1 Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelogenous leukemia [AML])
8.5.2 Myelodysplastic syndrome (MDS)
8.5.3 Treatment-related secondary malignancy

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

9. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

9.1. Olaparib

Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one

Other Names: Lynparza®

Classification: Olaparib is a small molecule antineoplastic poly (ADP-ribose) polymerase (PARP) enzyme inhibitor, including PARP1, PARP2, and PARP3.

Mechanism of Action: PARP enzymes are involved in DNA transcription, cell cycle regulation, and DNA repair. Olaparib is a potent oral PARP inhibitor that induces synthetic lethality in BRCA1/2 deficient tumor cells through the formation of double-stranded DNA breaks which cannot be accurately repaired, which leads to disruption of cellular homeostasis and cell death

CAS Registry Number: 763113-22-0

Molecular Formula: $C_{24}H_{23}FN_4O_3$ **M.W.:** 434.46

Approximate Solubility: Olaparib is a crystalline solid, is non-chiral and shows pH-independent low solubility across the physiological pH range.

9.1.1. **Olaparib Tablets**

How Supplied: Olaparib tablets are supplied by AstraZeneca Pharmaceuticals LP. Olaparib tablets for oral administration contain 100 mg or 150 mg of olaparib. Inactive ingredients in the tablet core are copovidone, mannitol, colloidal silicon dioxide and sodium stearyl fumarate. The tablet coating consists of hypromellose, polyethylene glycol 400, titanium dioxide, ferric oxide yellow and ferrosoferric oxide (150 mg tablet only).

150 mg tablets: green to green/grey, oval, bi-convex, film-coated tablet, with debossment 'OP150' on one side and plain on the reverse, are available in:

- Bottles of 60 tablets (NDC 0310-0679-60) and
- Bottles of 120 tablets (NDC 0310-0679-12).

100 mg tablets: yellow to dark yellow, oval, bi-convex, film-coated tablet, with debossment 'OP100'on one side and plain on the reverse, are available in:

- Bottles of 60 tablets (NDC 0310-0668-60) and
- Bottles of 120 tablets (NDC 0310-0668-12).

Storage: Store at 20ºC to 25ºC (68ºF to 77ºF), excursions permitted to 15ºC to 30ºC (59ºF to 86ºF). Store in original bottle to protect from moisture. 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.

Stability: Stability data from three production scale batches stored in the proposed packaging under long term conditions for up to 36 months (25°C / 60% RH) and under accelerated conditions (40°C / 75% RH) for 6 months according to the ICH guidelines has been provided. The 36 month data show no significant change with regards to the description, assay, organic impurities, polymorphic form, water content or particles size distribution for the samples stored at 25°C/60% RH, nor after 6 months at 40°C/75% RH and 6 months at 50°C/ambient humidity. Based on the available stability data, the proposed retest period of 48 months for olaparib when stored in LDPE bags at or below 30°C was considered acceptable.

Route of Administration: Oral administration per the protocol treatment schedule.

Method of Administration: Inform patients that olaparib should be taken twice daily with or without food. Instruct patients that if they miss a dose, they should take their next normal dose at the usual time. Swallow each tablet whole. Do not chew, crush, dissolve, or divide tablet. Do not take more than 4 tablets daily. Inform patients to avoid grapefruit, grapefruit juice, Seville oranges, Seville orange juice, pomelos, and starfruit while taking olaparib as these food products can alter the metabolism of olaparib. Inform patients not to substitute olaparib tablets (100 mg and 150 mg) with olaparib capsules (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation.

10. **BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES**

With the exception of patients who withdraw due to toxicity or withdraw consent, patients on this trial will ultimately develop PARP inhibitor resistant disease. This represents an important opportunity to collect biospecimens to evaluate resistance mechanisms and create patient derived xenograft tumor models for therapeutic development.

10.1 Integrated Laboratory Studies – Exploratory Objective

10.1.1 Tissue collection is optional. If the patient consents, archival tissue will be obtained from previous surgical resection. If the patient undergoes biopsy at the time of disease progression at part of standard of care practice, tissue will be requested from this biopsy as well.

10.1.2 Specimen Collection**: Pretreatment** tumor samples will be obtained from archived formalin-fixed, paraffin embedded (FFPE) tissue from the Pitt Biospecimen Core (PBC). Subject samples will undergo pathologic review with to ensure accurate diagnosis and tissue quality, >50% tumor and >50% viable cells, for subsequent molecular analysis. **Post-treatment** samples will be obtained at the time of detected disease recurrence or progression. A portion of each biopsy will undergo pathologic review as above.

10.1.3 Research Specimens: All specimens will be de-identified and clinical information stored in a locked computer database system. Research samples will be processed in the Buckanovich lab. If tissue is limited, samples will be snap frozen in liquid nitrogen and stored at -80°C for DNA/RNA isolation (QIAGEN® AllPrep DNA/RNA kit). For larger specimens (laparoscopic biopsy/resection), a portion of each sample will be (1) snap-frozen for RNA and DNA isolation, (2) disaggregated into single cells suspensions and live cell suspensions frozen, and (3) immediately transferred in DMEM media to Champions Oncology for PDX development.

10.1.4 Characterize genomic changes associated with olaparib resistance: For samples with limited tissue and therefore not amenable to PDX formation, we will use BROCA analysis (http://tests.labmed.washington.edu/BROCA#BROCA_Gene_List) on both pre and post-olaparib treatment samples to evaluate 69 different genes associated with HR defects. A total of 1.4 Mb are sequenced and the average coverage ranges from 320 to >1,000 sequencing reads per bp. Genomic regions are captured using biotinylated RNA oligonucleotides (SureSelect), prepared in paired-end libraries with ~200 bp insert size, and sequenced on an Illumina HiSeq2000. For samples for which PDX models are generated, we will perform whole genome sequencing (WGS) on the primary tissue, then compare WGS of primary tumors and PDX tumors. For specific genes in which we find molecular alterations, we will use knockdown and rescue assays in cell lines to validate olaparib resistance related to the identified target.

10.1.5 Characterize transcriptome changes associated with olaparib resistance*:* For an unbiased evaluation of mRNA expression changes associated with olaparib resistance, we will perform RNASeq (Novogene, utilizing Illumina's NovaSeq platform) with a random-primed cDNA synthesis non-strand-specific protocol. RNASeq will be compared between pre and post-olaparib treatment samples. Candidate drivers of resistance will be compared with BROCA results and then validated with knockin/knockout studies as above. Resistance mechanisms identified in the above studies can then be used in future work with the PDX models to test novel therapeutics to overcome PARP-I resistance.

10.1.6 Pharmacokinetics: To explore exposure-response relationships between olaparib

exposure and toxicity/efficacy. A steady-state trough sample will be obtained around day 28. Trough concentrations (if need be corrected for time since dosing) will be compared between patients with/without response and patients with/without toxicity. This assay will be performed at the UPMC Hillman Cancer Center Cancer Pharmacokineitc and Pharmacodynamics Facility. (CPPF). The published olaparib assay has successfully been implemented and is available (Nijenhuis et al. Journal of Chromatography B, 940 (2013) 121– 125). Note: plan the patient's day 28 visit such that their blood can be drawn at about the time they would otherwise take their dose, but **BEFORE** they take it. Ask patients to take bring their olaparib so they can take their dose after their PK blood draw. See appendix D for practical details.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of trial. Imaging CT scans and x-rays must be done ≤4 weeks prior to the start of therapy.

Procedure/Test	Pre- Study	Surveillance every 4 weeks	Day 1 of each cycle	Every 12 weeks	30 day follow- up*	Every 3 months
Informed consent	X					
Demographics	X					
Concurrent medications	X	X	X		X	
Medical history	X					
Physical exam [A]	X	X	X		X	
Vital signs [A]	X	X	X		X	
Height and Weight [A]	X	X	X		X	
Performance status [A]	X	X	X		X	
CBC w/diff, platelets [A]	X		X		X	
Serum chemistry [A,B]	X		X		X	
CA125 [A]	X	X	X		X	
PTT/PT/INR [C]	X					
EKG [C]	X					
Tumor Measurements [D]	X			X		
Baseline signs & symptoms	X					
Adverse event evaluation[E]	X	X	X		X	
Worry and Distress Measures[F]	X	X	X		X	
Quality of Life and Physical Function Measures[G]	X			X	X	
Financial Toxicity Measures[H]	X			X	X	
Urine or serum B-HCG for WOCBP [I]	X					
Tissue Collection[J]	X				X	
PK plasma sample[K]			X[K]			

BRCA testing[L]	X					
Survival Follow-up[M]						X

*Patients should be seen 30 days after completion of treatment to assess for resolution of toxicity

A. These procedures do not need to be repeated in cycle 1 if done pre-study within 7 days prior to start of protocol therapy.
B. Albumin, alkaline phosphatase, total bilirubin, direct bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium, phosphorus
C. Required pre-study, then as clinically indicated
D. Prior to olaparib initiation, imaging will only be done for doubling of nadir CA125 or per physician discretion for patient symptoms. Following initiation of olaparib, CT scans will be obtained every 12 weeks as part of surveillance. CT scans can be obtained for rising CA125 or physician preference for patient symptoms before scheduled routine surveillance.
E. Adverse event evaluation will include both the CTCAE and the PRO-CTCAE (See **Appendix D**).
F. Worry and distress measured via Assessment of Survivor Concerns (ASC) (See **Appendix E**) worry subscale and Impact of Event Scale (IES-R) (See **Appendix F**).
G. Health-related quality of life will be measured via The Functional Assessment of Cancer Therapy + Ovarian-specific scale (FACT-O) (See **Appendix G**) and physical function assessed through the PROMIS Physical Function-20a assesses self-reported performance of physical activities (See **Appendix H**).
H. Financial toxicity will be measured through a) monetary measure using the Modified Collection of Indirect and Nonmedical Direct Costs (COIN) (See **Appendix I**), b) objective measure of financial burden assessed using Barrera et al.'s Economic Hardship questionnaire (See **Appendix J**), and c) subjective measure of financial distress will be gauged using the Comprehensive Score for Financial Toxicity (COST Measure) (See **Appendix K**).
I. Pregnancy test for women of childbearing potential (WOCBP) must be done within 24 hours prior to initiation of olaparib.
J. Tissue collection is not mandatory. If permission granted, tissue prior to initiation on olaparib will be obtained from archival stores. If patient undergoes biopsy at the time of progression as part of standard of care, tissue will be collected after routine processing.
K. A mandatory trough plasma sample will be obtained only once at approximately 28 days after initiation of treatment (See **Appendix L**).
L. BRCA testing required (Results not needed for registration
M. Chart review or office visit every 3 months for 18 months from time of enrollment

12. MEASUREMENT OF EFFECT

Although not all patients will have measurable disease, patients with partial response to the previous platinum-based therapy are eligible for this study, and they will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients will be assessed by standard criteria. For this study, patients will undergo a clinical assessment every 4 weeks while receiving olaparib. Tumor response will be evaluated at 12 week intervals.

12.1. Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. 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.

12.1.1. Definitions

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

Evaluable for objective response by RECIST. Patients who have received at least 1 cycle of therapy and have had their disease re-evaluated with a 3-month post treatment CT 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.)

Evaluable for objective response by CA-125. Patients who have received at least 1 cycle of therapy, have a CA-125 before treatment below the upper limit of the normal (for values above this limit, any increase in a second sample has to be <15% increase) and have had their disease re-evaluated with monthly CA125, 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.)

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, 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.

12.1.2. 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 ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] 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.

12.1.3. 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 (≥1 cm) 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 (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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: 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 have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. 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 [*JNCI* 92:1534-1535, 2000].

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 that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4. Response Criteria

12.1.4.1. 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 (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum 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 (0.5 cm). (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 diameters while on study.

12.1.4.2 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 [<1 cm] 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).

12.1.4.3 Evaluation Based on CA125

Complete Response (CR): Normalization of CA-125 levels. The response must be confirmed and maintained for at least 28 days. No new or progressive disease on imaging.

Partial Response (PR): At least a 50% reduction in CA-125 levels from a pretreatment sample but not reaching normalization. The response must be confirmed and maintained for at least 28 days. No new or progressive disease on imaging.

Progressive Disease (PD):

- Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart or
- Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart or

- Patients with CA-125 in the reference range before treatment must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart
- Response determined via measurable disease (measurement of target and non-target lesions) takes precedence over CA-125 criteria

Stable Disease (SD): CA-125 fluctuations not fitting above criteria

12.1.5 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.

12.1.5.1 Evaluation of Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
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.
**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-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		

13. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

13.1. Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the overall conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s).

All studies are also reviewed in accordance with the UPMC Hillman Cancer Center data safety monitoring plan (DSMP).

13.2. Data Reporting

13.2.1. Responsibility for Data Submission

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in the UPMC Hillman Cancer Center Data Safety Monitoring Board (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 5.0 or Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE). All study treatment associated adverse events that are both serious and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close, the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center DSMC, which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Both the UPMC Hillman Cancer Center DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

Primary endpoint is defined as the time to next therapy from completion of platinum-based therapy for treatment of recurrence until initiation of post-olaparib treatment. Based on Ledermann et al,[29] the expected median time to progression on olaparib following platinum response is 8.4 months for a cohort with 22% *BRCA* mutation prevalence.

Secondary endpoints
Progression-free survival is defined as the time from enrollment until detected recurrence or progression of disease, via RECISTv1.1, or death from any cause.

- Overall survival as defined as the time from enrollment to death from any cause.
- Toxicity rates defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
- Response rate as defined by RECIST or CA-125 and stratified by *BRCA* mutation status.
- Patient-reported adverse events using the NCI Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) (See Appendix
- Health-related quality of life measured via The Functional Assessment of Cancer Therapy + Ovarian-specific scale (FACT-O)
- Physical function assessed through the PROMIS Physical Function-20a assesses self-reported performance of physical activities
- Worry and distress measured via Assessment of Survivor Concerns (ASC) Worry Subscale and Impact of Event Scale (IES-R)
- Financial toxicity measured through
  a) monetary measure using the Modified Collection of Indirect and Nonmedical Direct Costs (COIN),
  b) objective measure of financial burden assessed using Barrera et al.'s Economic Hardship questionnaire[51], and
  c) subjective measure of financial distress will be gauged using the Comprehensive Score for Financial Toxicity (COST Measure).
- Exposure measured through quantitating olaparib by LC-MS/MS in a trough sample.

Racial Categories	Ethnic Categorie s		Total
	Not Hispanic or Latino	Hispanic or Latino	
	Female	Female	
American Indian/ Alaska Native	0	0	**0**

Racial Categories	Ethnic Categories		Total
	Not Hispanic or Latino	Hispanic or Latino	
	Female	Female	
Asian	3	0	**3**
Native Hawaiian or Other Pacific Islander	0	0	**0**
Black or African American	7	0	**7**
White	65	0	**65**
More Than One Race	0	0	**0**
Total	**75**	**0**	**75**

13.2 SAMPLE SIZE/ACCRUAL RATE

Study 19 is the only PARP inhibitor maintenance trial in the platinum sensitive recurrent setting to report both PFS and OS data. Median progression-free survival was 8.4 months in the olaparib group versus 4.8 months in the placebo group (hazard ratio for progression or death, 0.35; 95% confidence interval [CI], 0.25 to 0.49; P<0.001). The secondary end point of time to progression according to the RECIST guidelines or CA-125 level, whichever showed earlier progression, was also significantly longer in the olaparib group than in the placebo group (median, 8.3 months vs. 3.7 months; hazard ratio for progression, 0.35; 95% CI, 0.25 to 0.47; P<0.001). There was no statistically significant OS advantage noted for those treated with olaparib; for the entire population median OS was 29.8-months-[95%-CI-26·9–35·7]-in the olaparib arm vs 27.8 months-[24·9–33·7] in the placebo arm. For those patients evaluable for response (n=61), there were 16 (26.2%) either PR or CR by RECIST and 1 (1.6%) by CA125[29].

Using the reported data from Study 19, we will assess whether delaying olaparib until biochemical relapse will increase the median time to next treatment by ~3 months (from 8 to 11 months). We assume 3-4 patients can be accrued/month and that the *BRCA* mutation

prevalence will be ~20% and thereby be comparable to the historical control group. With 2 years of accrual and 18 months of additional follow up, we will require 75 eligible patients. This will allow 90% power for a level 0.10 one-sided one sample exponential test to detect an improvement in median time to next treatment from 8 to 11 months. Due to the possibility of lost to long-term follow-up, we plan to accrue an additional 10% of the targeted accrual. Therefore, the sample size for this study will be approximately 83 patients in order to successfully accrue 75 evaluable patients.

13.3 DATA ANALYSIS

13.3.1 Analysis Sets

Evaluable patients: patients who meet all of the protocol inclusion/exclusion criteria and begin treatment with the protocol regimen.

Safety set: data from all evaluable patients who receive initial treatment of the study treatment will be used in the analysis of safety.

Efficacy set: data from all evaluable patients who receive initial treatment of the study treatment will be used in the analysis of efficacy endpoints.

Exploratory set: the data from all study-eligible patients (i.e. those meeting all of the protocol inclusion/exclusion criteria) who begin the study treatment and have tissue samples taken will be used in the analyses to address the correlative biomarker aims.

13.3.2 Analysis of Baseline Demographic Variables

Baseline descriptive statistics on all evaluable patients will be provided for demographic variables (age, BMI, race/ethnicity), ECOG performance status, disease stage and status at the time of enrollment (stable disease, progressive disease), and treatment regimens previously used.

13.3.3 Analysis of Safety Endpoints

The NCI common terminology criteria for adverse events (CTCAE 5.0) will be used to evaluate toxicity; we will consider a toxicity to be an adverse event that is possibly, probably or definitely related to treatment. The maximum grade of toxicity for each category of interest will be recorded for each patient and the summary results will be tabulated by category and grade. Statistics on the number of cycles received by patients and any dose reductions will also be tabulated.

13.3.4 Analysis of Efficacy Endpoints

Allowing 18 months of follow-up following the last patient accrual, time to next treatment will be estimated by the Kaplan-Meier method. Median time to next treatment will be estimated with 90% confidence intervals. The maximum likelihood estimate of the hazard rate (hazard of next treatment) will be calculated and used to conduct a one-tailed

exponential test at level alpha = .10. This will test the hypothesis that time to next treatment is increased over that expected for olaparib without delay (this assumes the data follow an exponential distribution, otherwise, an alternate parametric test or a one sample log rank test will be used). Toxicities will be summarized by grade, frequency and attribution to olaparib. Median progression-free survival (PFS) and overall survival (OS) will be estimated using the Kaplan Meir method. The Kaplan-Meier method with a log rank test will be applied to test differential response by mutation status. We will estimate the response rate utilizing RECIST and/or GCIG criteria. For those patients with measurable disease and elevated CA125, both RECIST and GCIG criteria will be utilized. For those without measurable disease, GCIG criteria alone will be used to record response. Overall response will be defined as the number of patients with best overall response of CR and PR. The effect of treatment will be reported with its supporting 90% confidence interval.

13.3.5 Analysis of Patient Reported Outcomes, Quality of Life and Financial Toxicity Endpoints

Additional **Secondary Endpoints** include a series of quality of life instruments and financial toxicity measures. These instruments will be administered starting at onset of trial enrollment and periodically thereafter. Patient reported adverse events, worry and distress (3 instruments measured every 4 weeks), health related quality of life, physical functioning and financial toxicity (5 instruments measured every 12 weeks) will provide data for longitudinal analysis with mixed effects linear models. We will focus on change over time particularly between the two treatment periods, pre and post olaparib. Our linear mixed effects models will emphasize random coefficients that allow non-linear profiles, typically polynomial regression, restricted cubic splines or piecewise linear splines with a knot to represent the time of starting olaparib. These models will permit us to estimate whether quality of life and financial toxicity change over the course of the clinical trial and, in particular, whether the observed change suggests a shift that is consistent with the start of olaparib therapy.

For drug exposure measured through quantitating olaparib by LC-MS/MS in a trough sample, trough concentrations between groups will be compared with non-parametric Wilcoxon signed rank test with significance set at $P<0.05$. If significant, we may explore ROC analyses.

13.3.6 Analysis of Exploratory Endpoints

DNA: BROCA or whole genome sequencing for mutational changes will be assessed in pre and post- olaparib treatment. Variant changes over time will be reported descriptively. These will be assessed against reference genome to determine pathogenic variants.

RNA: RNA-Seq analysis will be performed per a recent comparative and guideline paper[55], sequencing reads will be examined for data quality by FastQC, and aligned, assembled and annotated (gene-based and isoform-based) using HISAT2, StringTie and Ballgown[56]. Differential expression analysis based on count data will be performed by DESeq2[57]. Low expressed genes will be filtered (25% of genes with smallest sum of counts across all samples). Assuming significance level at 0.05, n=40 samples (20 each pre/post therapy) standard deviation at 0.1, we will have >99%. statistical power to detect a difference for a given gene with effect size=0.8. When we account for multiple testing for 10,000 genes, we still have 70% statistical power to detect a difference of effect size 3 at

Family-Wise Error Rate (FWER) of 0.05. Using False Discovery Rate (FDR) for multiple testing control (e.g. using Benjamini-Hochberg procedure) can only increase the power.

REFERENCES

1. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.
2. Jayson GC, Kohn EC, Kitchener HC, et al. Ovarian cancer. Lancet. 2014 Oct 11;384(9951):1376-88.
3. Markman M, Liu PY, Moon J, Monk BJ, Copeland L, Wilczynski S, Alberts D. Impact on survival of 12 versus 3 monthly cycles of paclitaxel (175 mg/m2) administered to patients with advanced ovarian cancer who attained a complete response to primary platinum-paclitaxel: Follow-up of a Southwest Oncology Group and Gynecologic Oncology Group phase 3 trial. Gynecol Oncol 114: 195-8, 2009.
4. Copeland JC, Brady MF, Burger RA, Rodgers WH, Huang H, Cella D, Fowler JM, Walker LJ, Krishnansu ST, Bender DP, Morris RT, Lowery WJ, Miller DS, Dewdney SB, Spirtos NM, Lele SB, Guntupalli SR, Ueland FR, Glasser GE, Mannel RS, DiSaia PJ. A phase III trial of maintenance therapy in women with advanced ovarian/Fallopian tube/peritoneal cancer (O/PC/FT) after a complete clinical response (CCR) to first-line therapy – an nrg oncology study. Scientific Plenary VI. Presented at the 2017 Annual Meeting for Women's Cancers. March 14, 2017, National Harbor, Washington DC.
5. Chen H, Fang F, Liu GJ, Xie HY, Zou J, Feng D. Maintenance chemotherapy for ovarian cancer (Review). Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD007414
6. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, Boente M, Birrer MJ, Liang SX, Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer.N Engl J Med. 2011 Dec;365(26):2473-83.
7. Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Park-Simon TW, Rustin G, Joly F, Mirza MR, Plante M, Quinn M, Poveda A, Jayson GC, Stark D, Swart AM, Farrelly L, Kaplan R, Parmar MK, Perren TJ, ICON7 trial investigators. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol. 2015 Aug;16(8):928-36. Epub 2015 Jun 23.
8. Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015 Oct;139(1):10-6.
9. Coleman RL, Brady MF, Herzog TJ, et al. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). Scientific Plenary #3 Presented at the 2015 Annual Meeting for Women's Cancers. March 28, 2015. Chicago, IL.
10. Incorporation of pazopanib in maintenance therapy of ovarian cancer. du Bois A, Floquet A, Kim JW, Rau J, Del Campo JM, Friedlander M, Pignata S, Fujiwara K, Vergote I, Colombo N, Mirza MR, Monk BJ, Kimmig R, Ray-Coquard I, Zang R, Diaz-Padilla I, Baumann KH, Mouret-Reynier MA, Kim JH, Kurzeder C, Lesoin A, Vasey P, Marth C, Canzler U, Scambia G, Shimada M, Calvert P, Pujade-Lauraine E, Kim BG, Herzog TJ, Mitrica I, Schade-Brittinger C, Wang Q, Crescenzo R, Harter P Incorporation of pazopanib in maintenance therapy of

ovarian cancer. J Clin Oncol. 2014;32(30):3374.
11. DuBois A, Kristensen G, Ray-Coquard I, et al. AGO-OVAR 12: A randomized placebo-controlled GCIG/ENGOT intergroup phase III trial of standard frontline chemotherapy +/- nintedanib for advanced ovarian cancer. Int J Gynecol Oncol 2013; 23 (suppl 1). Oral abstract.
12. Despierre E, Vergote I, Anderson R, Coens C, Katsaros D, Hirsch FR, Boeckx B, Varella-Garcia M, Ferrero A, Ray-Coquard I, Berns EM, Casado A, Lambrechts D, Jimeno A; European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group (EORTC-GCG); Groupe d'Investigateurs Nationaux pour les Etudes des Cancers de l'Ovaire (GINECO); Austrian Arbeitsgemeinschaft für Gynäkologische Onkologie (A-AGO); National Cancer Research Institute (NCRI); Australia New Zealand Gynaecological Oncology Group (ANZGOG); Mario Negri Gynecologic Oncology group (MaNGO). Epidermal Growth Factor Receptor (EGFR) Pathway Biomarkers in the Randomized Phase III Trial of Erlotinib Versus Observation in Ovarian Cancer Patients with No Evidence of Disease Progression after First-Line Platinum-Based Chemotherapy. Target Oncol. 2015 Dec;10(4):583-96.
13. GD Hall, JM Brown, RE Coleman , et al : Maintenance treatment with interferon for advanced ovarian cancer: Results of the Northern and Yorkshire Gynaecology Group randomised phase III study Br J Cancer 91: 621– 626, 2004
14. J Berek, P Taylor, W McGuire , etal : Oregovomab maintenance monoimmunotherapy does not improve outcomes in advanced ovarian cancer J Clin Oncol 27: 418– 425, 2009
15. Sabbatini P, Harter P, Scambia G, Sehouli J, Meier W, Wimberger P, Baumann KH, Kurzeder C, Schmalfeldt B, Cibula D, Bidzinski M, Casado A, Martoni A, Colombo N, Holloway RW, Selvaggi L, Li A, del Campo J, Cwiertka K, Pinter T, Vermorken JB, Pujade-Lauraine E, Scartoni S, Bertolotti M, Simonelli C, Capriati A, Maggi CA, Berek JS, Pfisterer J. Abagovomab as maintenance therapy in patients with epithelial ovarian cancer: a phase III trial of the AGO OVAR, COGI, GINECO, and GEICO--the MIMOSA study. 2013 Apr 20;31(12):1554-61
16. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012;30(21):2654e63.
17. Zhang S, Royer R, Li S, McLaughlin JR, Rosen B, Risch HA, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol 2011;121(2):353e7.
18. Janavicius R, Rudaitis V, Mickys U, Elsakov P, Griskevicius L. Comprehensive BRCA1 and BRCA2 mutational profile in Lithuania. Cancer Genet 2014;207(5):195e205.
19. Song H, Cicek MS, Dicks E, Harrington P, Ramus SJ, Cunningham JM, et al. The contribution of deleterious germline mutations in BRCA1, BRCA2 and the mismatch repair genes to ovarian cancer in the population. Hum Mol Genet 2014;23(17): 4703e9.
20. Vicus D, Finch A, Cass I, Rosen B, Murphy J, Fan I, et al. Prevalence of BRCA1 and BRCA2 germ line mutations among women with carcinoma of the fallopian tube. Gynecol Oncol 2010;118(3):299e302.
21. Aguilar-Quesada, R., Munoz-Gamez, J.A., Martin-Oliva, D., Peralta, A., Valenzuela, M.T., Matinez-Romero, R. et al. Interaction between ATM and PARP-1 in response to DNA damage and sensitization of ATM deficient cells through PARP inhibition. BMC Mol. Biol. 2007; 8: 29
22. Buisson, R., Dion-Cote, A.M., Coulombe, Y., Launay, H., Cai, H., Stasiak, A.Z. et al. Cooperation of breast cancer proteins PALB2 and piccolo BRCA2 in stimulating homologous recombination. Nat. Struct. Mol. Biol. 2010; 17: 1247–1254
23. Rafnar, T., Gudbjartsson, D.F., Sulem, P., Jonasdottir, A., Sigurdsson, A., Jonasdottir, A. et al. Mutations in BRIP1 confer high risk of ovarian cancer. Nat. Genet. 2011; 43: 1104–1107

24. Walsh, T., Casadei, S., Lee, M.K., Pennil, C.C., Nord, A.S., Thornton, A.M. et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc. Natl. Acad. Sci. U. S. A. 2011; 108: 18032–18037
25. Kaye SB, Lubinski J, Matulonis U, Ang JE, Gourley C, Karlan BY, Amnon A, Bell-McGuinn KM, Chen LM, Friedlander M, Safra T, Vergote I, Wickens M, Lowe ES, Carmichael J, Kaufman B. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol. 2012 Feb 1;30(4):372-9.
26. Kaufman, B., Shapira-Frommer, R., Schmutzler, R.K., Audeh, M.W., Friedlander, M., Balmana, J. et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J. Clin. Oncol. 2015; 33: 244–250
27. Kristeleit R, Shapiro GI, Burris HA, Oza AM, LoRusso P, Patel MR, et al. A Phase I-II study of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2 -mutated ovarian carcinoma or other solid tumors. Clin Cancer Res 2017; 23(15): 4095-106.
28. Swisher, E.M., Lin, K.K., Oza, A.M., Scott, C.L., Giordano, H., Sun, J. et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol. 2017; 18: 75–87
29. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott C, Meier W, Shapira-Frommer R, Safra T, Matei D, Macpherson E, Watkins C, Carmichael J, Matulonis U. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012 Apr 12;366(15):1382-92.
30. Pujade-Lauraine, E., Ledermann, J.A., Selle, F., Gebski, V., Penson, R.T., Oza, A.M. et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017; 18: 1274–1284
31. Coleman, R.L., Oza, A.M., Lorusso, D., Aghajanian, C., Oaknin, A., Dean, A. et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. (pii: S0140-6736(17)32440-6)Lancet. 2017;
32. Mirza, M.R., Monk, B.J., Herrstedt, J., Oza, A.M., Mahner, S., Redondo, A. et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N. Engl. J. Med. 2016; 375: 2154–2164.
33. Gordon SW and Temkin SM. Is There a Role for Maintenance PARP for Patients With Platinum-Sensitive Ovarian Cancer? Current Controversies in Oncology. ASCO Connection. Published Apr 25, 2018. https://connection.asco.org/magazine/current-controversies-oncology/there-role-maintenance-parp-patients-platinum-sensitive.
34. Poly ADP-Ribose Polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value Final Evidence Report September 28, 2017. Prepared for CEPAC. ©Institute for Clinical and Economic Review, 2017 https://icer-review.org/wp-content/uploads/2017/02/MWCEPAC_OVARIAN_FINAL_EVIDENCE_REPORT_10112017.pdf
35. Rustin GJ, van der Burg ME, Griffin CL, Guthrie D, Lamont A, Jayson GC, Kristensen G, Mediola C, Coens C, Qian W, Parmar MK, Swart AM; MRC OV05; EORTC 55955 investigators. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet. 2010 Oct 2;376(9747):1155-63.
36. Norquist, B., Wurz, K.A., Pennil, C.C., Garcia, R., Gross, J., Sakai, W. et al. Secondary somatic mutations restoring BRCA1/2 predict chemotherapy resistance in hereditary ovarian carcinomas. J. Clin. Oncol. 2011; 29: 3008–3015

37. Barber, L.J., Sandhu, S., Chen, L., Campbell, J., Kozarewa, I., Fenwick, K. et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. J. Pathol. 2013; 229: 422–429
38. Kondrashova O, Nguyen M, Shield-Artin K, Tinker AV, Teng NNH, Harrell MI, et al. Secondary Somatic Mutations Restoring RAD51C and RAD51D Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma. Cancer Discov. 2017 Sep;7(9):984-998.
39. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guidelines (version 1.1). European Journal of Cancer 45(2009) 228-247.
40. Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, du Bois A, Kristensen G, Jakobsen A, Sagae S, Greven K, Parmar M, Friedlander M, Cervantes A, Vermorken J. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG).Int J Gynecol Cancer 2011;21:419-23.
41. National Institutes of Health, National Cancer Institute. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Rockville (MD): NCI Available from: https://healthcaredelivery.cancer.gov/pro-ctcae/.
42. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570-9.
43. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, Webster K, Cella D, Hu S, Gershenson DM. Reliability and validity of the functional assessment of cancer therapy-ovarian. J Clin Oncol. 2001 Mar 15;19(6):1809-17.
44. Rose M, Bjorner JB, Gandek B, Bruce B, Fries JF, Ware JE. The PROMIS Physical Function Item Bank Was Calibrated to a Standardized Metric and Shown to Improve Measurement Efficiency. J Clin Epidemiol. 2014 May; 67(5): 516–526.
45. Gotay CC, Pagano IS. Assessment of Survivor Concerns (ASC): A newly proposed brief questionnaire. Health Qual Life Outcomes. 2007; 5: 15.
46. Hershman DL[1], Greenlee H, Awad D, Kalinsky K, Maurer M, Kranwinkel G, Brafman L, Jayasena R, Tsai WY, Neugut AI, Crew KD. Randomized controlled trial of a clinic-based survivorship intervention following adjuvant therapy in breast cancer survivors. Breast Cancer Res Treat. 2013 Apr;138(3):795-806.
47. Thewes, B., Butow, P., Bell, M. L., Beith, J., Stuart-Harris, R., Grossi, M.,Dailey, D. (2012). Fear of cancer recurrence in young women with a history of early-stage breast cancer: A cross-sectional study of prevalence and association with health behaviours. Supportive Care in Cancer, 20, 2651-2659.
48. John M. Salsman,[1,2,*] Benjamin D. Schalet,[1] Michael A. Andrykowski,[3] and David Cella[1,2] The impact of events scale: a comparison of frequency versus severity approaches to measuring cancer-specific distress. Psychooncology. 2015 Dec; 24(12): 1738–1745.
49. Andrea Vodermaier, Wolfgang Linden, and Christopher Siu Screening for Emotional Distress in Cancer Patients: A Systematic Review of Assessment Instruments J Natl Cancer Inst. 2009 Nov 4; 101(21): 1464–1488.
50. Sherman EJ[1], Pfister DG, Ruchlin HS, Rubin DM, Radzyner MH, Kelleher GH, Slovin SF, Kelly WK, Scher HI. The Collection of Indirect and Nonmedical Direct Costs (COIN) form: a new tool for collecting the invisible costs of androgen independent prostate carcinoma. Cancer. 2001 Feb 15;91(4):841-53.

51. Barrera M Jr[1], Caples H, Tein JY. The psychological sense of economic hardship: measurement models, validity, and cross-ethnic equivalence for urban families. Am J Community Psychol. 2001 Jun;29(3):493-517.
52. de Souza JA[1], Yap BJ, Hlubocky FJ, Wroblewski K, Ratain MJ, Cella D, Daugherty CK. The development of a financial toxicity patient-reported outcome in cancer: The COST measure. Cancer. 2014 Oct 15;120(20):3245-53.
53. de Souza JA, Yap BJ, Wroblewski K, Blinder V, Araújo FS, Hlubocky FJ, Nicholas LH, O'Connor JM, Brockstein B, Ratain MJ, Daugherty CK, Cella D. Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the COmprehensive Score for financial Toxicity (COST). Cancer. 2017 Feb 1;123(3):476-484.
54. Silva, I.A., et al., Aldehyde dehydrogenase in combination with CD133 defines angiogenic ovarian cancer stem cells that portend poor patient survival. Cancer Res, 2011. **71**(11): p. 3991-4001.
55. Sahraeian, S.M.E., et al., Gaining comprehensive biological insight into the transcriptome by performing a broad-spectrum RNA-seq analysis. Nat Commun, 2017. **8**(1): p. 59.
56. Pertea, M., et al., Transcript-level expression analysis of RNA-seq experiments with HISAT, StringTie and Ballgown. Nat Protoc, 2016. **11**(9): p. 1650-67.
57. Love, M.I., W. Huber, and S. Anders, Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol, 2014. **15**(12): p. 550.

APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: PATIENT DRUG DIARY: OLAPARIB

Today's Date _____ Cycle # _____
Patient Name Patient Study ID

1. Complete one form for each cycle (28 days).
2. Record the date, the number of tablets you took, and when you took them.
3. Bring your pill bottles (including empty bottles) and this form to every appointment.
4. Do not chew, dissolve, or crush medications. DO NOT make up vomited doses.
5. If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose.
6. The first row in the table below is an EXAMPLE ROW for how to complete this diary.

OLAPARIB
Take (number) mg and (number) mg tablets twice a day 12 hours apart.

Day	**Date**	**100mg**	**150mg**	**AM**	**PM**
1	**9/1/2019**	**0**	**2**	**8:00**	**8:00**
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
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27					
28					

Patient's Signature: _____ Date: _____
Physician/Nurse/Data Manager's Signature _____
Date

APPENDIX C: Possible Interactions with Other Drugs and Herbal Supplements

CYP3A4 Inhibitors

Strong Inhibitors (prohibited)	Moderate Inhibitors (use with caution avoid if possible)	Weak Inhibitors (use with caution avoid if possible)
Amprenavir[1]	Amiodarone[1]	Chloramphenicol[2]
Atazanavir[1]	Aprepitant	Ciprofloxacin[2]
Clarithromycin	Cimetidine[1]	Diethyldithiocarbamate[2]
Conivaptan[1]	Clotrimazole[1]	Fluvoxamine[2]
Delavirdine[1]	Cyclosporine[1]	Gestodene[2]
Fosamprenavir[1]	Desipramine[1] Doxycycline[1]	Mibefradil[2]
Fospropofol[1]	Efavirenz[1]	Mifepristone
Imatinib[1]	Erythromycin	Norfluoxetine[2]
Indinavir	Fluconazole	Star fruit[2]
Isoniazid[1]	Fosaprepitant[1]	Troleandomycin[2]
Itraconazole	Grapefruit juice	
Ketoconazole	Haloperidol[1]	
Miconazole[1]	Lidocaine[1]	
Nefazodone	Metronidazole[1]	
Nelfinavir	Norfloxacin1	
Nicardipine[1] Posaconazole[1]	Sertraline[1]	
Propofol[1]	Tetracycline[1]	
Quinidine[1]	Verapamil	
Ritonavir	Voriconazole[1]	
Saquinavir[2]		
Telithromycin		

1 Cited in Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Drug Information Handbook 20th ed. Hudson, OH; LexiComp Inc. 2011-2012: 1810-1818

2 Cited in Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed Nov 2011. Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

CYP3A4 Inducers

Armodafenil[1]	Fosphenytoin[1]	Oxcarbazepine	Rifabutin
Barbiturates[2]	Glucocorticoids[2] (see	Pentobarbital[1]	Rifampin
Bosentan[1]	note)	Phenobarbital	Rifapentine[1]
Carbamazepine	Modafinil2	Phenytoin	St. John's wort[2]
Dexamethasone[1]	Nafcillin1	Pioglitazone[2]	Troglitazone[3]
Efavirenz	Nevirapine	Primidone[1]	

Note: Topical steroids are permitted. Systemic steroids may be acceptable after discussion with PI.

1 Cited in Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Drug Information Handbook 20th ed. Hudson, OH; LexiComp Inc. 2011-2012: 1810-1818

2 Cited in Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed Nov 2011.

3 Weak inhibitor per Lacy et al. May be used with caution. Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

APPENDIX D: NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 6 August 2019

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an in the one box that best describes your experiences over the past 7 days…

1. In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

2. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

3. In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

4. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

5. In the last 7 days, how OFTEN did you have NAUSEA?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

6. In the last 7 days, how OFTEN did you have VOMITING?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

7. In the last 7 days, how OFTEN did you have HEARTBURN?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

8. In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

9. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

10. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

11. In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

12. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

13. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

14. In the last 7 days, how OFTEN did you have ARM OR LEG SWELLING?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, what was the SEVERITY of your ARM OR LEG SWELLING at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

15. In the last 7 days, did you have any RASH?
○ Yes ○ No

16. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

17. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

18. In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

19. In the last 7 days, what was the SEVERITY of your PROBLEMS WITH CONCENTRATION at their WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did PROBLEMS WITH CONCENTRATION INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

20. In the last 7 days, what was the SEVERITY of your PROBLEMS WITH MEMORY at their WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did PROBLEMS WITH MEMORY INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

21. In the last 7 days, how OFTEN did you have a HEADACHE?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

22. In the last 7 days, how OFTEN did you have ACHING MUSCLES?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

23. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

24. In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

25. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

26. In the last 7 days, how OFTEN did you feel ANXIETY?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

27. In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

28. In the last 7 days, what was the SEVERITY of your PAIN OR BURNING WITH URINATION at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

29. In the last 7 days, how OFTEN did you feel an URGE TO URINATE ALL OF A SUDDEN?
○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, how much did SUDDEN URGES TO URINATE INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

30. In the last 7 days, were there times when you had to URINATE FREQUENTLY?

○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly
In the last 7 days, how much did FREQUENT URINATION INTERFERE with your usual or daily activities?
○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

31. In the last 7 days, what was the SEVERITY of your DECREASED SEXUAL INTEREST at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
○ Not sexually active
○ Prefer not to answer

Do you have any other symptoms that you wish to report?
○ Yes ○ No
Please list any other symptoms:
1. In the last 7 days, what was the SEVERITY of this symptom at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
2. In the last 7 days, what was the SEVERITY of this symptom at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
3. In the last 7 days, what was the SEVERITY of this symptom at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
4. In the last 7 days, what was the SEVERITY of this symptom at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe
5. In the last 7 days, what was the SEVERITY of this symptom at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

APPENDIX E: Assessment of Survivor Concerns (ASC)

Below is a list of worries people sometimes have after a diagnosis of cancer. Please indicate how much worry you experience with each of the following topics.

I worry about…	Not at all 1	A little bit 2	Somewhat 3	Very much 4
1. Future diagnostic tests	Δ	Δ	Δ	Δ
2. Another type of cancer	Δ	Δ	Δ	Δ
3. My cancer coming back	Δ	Δ	Δ	Δ

APPENDIX F: IMPACT OF EVENT SCALE- REVISED

INSTRUCTIONS: Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you

DURING THE PAST SEVEN DAYS with respect to _____, which occurred on _____. How much were you distressed or bothered by these difficulties?

Not at all = 0	A little bit = 1	Moderately = 2	Quite a bit = 3	Extremely = 4

1. Any reminder brought back feelings about it.
2. I had trouble staying asleep.
3. Other things kept making me think about it.
4. I felt irritable and angry.
5. I avoided letting myself get upset when I thought about it or was reminded of it.
6. I thought about it when I didn't mean to.
7. I felt as if it hadn't happened or wasn't real.
8. I stayed away from reminders of it.
9. Pictures about it popped into my mind.
10. I was jumpy and easily startled.
11. I tried not to think about it.
12. I was aware that I still had a lot of feelings about it, but I didn't deal with them.
13. My feelings about it were kind of numb.
14. I found myself acting or feeling like I was back at that time.
15. I had trouble falling asleep.
16. I had waves of strong feelings about it.
17. I tried to remove it from my memory.
18. I had trouble concentrating.
19. Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart.
20. I had dreams about it.
21. I felt watchful and on-guard.
22. I tried not to talk about it.

The Intrusion subscale is the **MEAN** item response of items 1, 2, 3, 6, 9, 14, 16, 20. Thus, scores can range from 0 through 4.

The Avoidance subscale is the **MEAN** item response of items 5, 7, 8, 11, 12, 13, 17, 22. Thus, scores can range from 0 through 4.

The Hyperarousal subscale is the **MEAN** item response of items 4, 10, 15, 18, 19, 21. Thus, scores can range from 0 through 4.

Citations: Weiss, D.S. & Marmar, C.R. (1997). The Impact of Event Scale-Revised. In J.P. Wilson, & T. M. Keane (Eds.), *Assessing Psychological Trauma and PTSD: A Practitioner's Handbook*. (pp. 399-411). New York: Guilford.
Weiss, D. S. (2004). The Impact of Event Scale-Revised. In J. P. Wilson, & T. M. Keane (Eds.), *Assessing psychological trauma and PTSD: A practitioner's handbook* (2nd ed., pp. 168-189). New York: Guilford Press.

APPENDIX G: FACT-O (Version 4)

English (Universal) 16 November 2007

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
PHYSICAL WELL-BEING					
GP1 I have a lack of energy	0	1	2	3	4
GP2 I have nausea	0	1	2	3	4
GP3 Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4 I have pain	0	1	2	3	4
GP5 I am bothered by side effects of treatment	0	1	2	3	4
GP6 I feel ill	0	1	2	3	4
GP7 I am forced to spend time in bed	0	1	2	3	4
SOCIAL/FAMILY WELL-BEING					
GS1 I feel close to my friends	0	1	2	3	4
GS2 I get emotional support from my family	0	1	2	3	4
GS3 I get support from my friends	0	1	2	3	4
GS4 My family has accepted my illness	0	1	2	3	4
GS5 I am satisfied with family communication about my illness	0	1	2	3	4
GS6 I feel close to my partner (or the person who is my Main support)	0	1	2	3	4
Q1 *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*					
GS7 I am satisfied with my sex life	0	1	2	3	4
EMOTIONAL WELL-BEING Not					
GE1 I feel sad	0	1	2	3	4
GE2 I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3 I am losing hope in the fight against my illness	0	1	2	3	4
GE4 I feel nervous	0	1	2	3	4
GE5 I worry about dying	0	1	2	3	4
GE6 I worry that my condition will get worse	0	1	2	3	4
FUNCTIONAL WELL-BEING					
GF1 I am able to work (include work at home)	0	1	2	3	4
GF2 My work (include work at home) is fulfilling	0	1	2	3	4
GF3 I am able to enjoy life	0	1	2	3	4
GF4 I have accepted my illness	0	1	2	3	4
GF5 I am sleeping well	0	1	2	3	4

GF6 I am enjoying the things I usually do for fun.....0 1 2 3 4
GF7 I am content with the quality of my life right now 0 1 2 3 4

ADDITIONAL CONCERNS

O1 I have swelling in my stomach area..... 0 1 2 3 4
C2 I am losing weight.....0 1 2 3 4
C3 I have control of my bowels.....0 1 2 3 4
O2 I have been vomiting.....0 1 2 3 4
B5 I am bothered by hair loss 0 1 2 3 4
C6 I have a good appetite 0 1 2 3 4
C7 I like the appearance of my body 0 1 2 3 4
BMT5 I am able to get around by myself.....0 1 2 3 4
B9 I am able to feel like a woman 0 1 2 3 4
O3 I have cramps in my stomach area..... 0 1 2 3 4
BL4 I am interested in sex. 0 1 2 3 4
BMT7 I have concerns about my ability to have children.....0 1 2 3 4

APPENDIX H: PROMIS

PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities – Short Form 6a

Ability to Participate in Social Roles and Activities – Short Form 6a

Please respond to each item by marking one box per row. Never		Rarely	Sometimes	Usually		Always
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER15_CaPS	I have to limit the things I do for fun with others.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER28r1	I have to limit my regular activities with friends	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Satisfaction with Social Roles and Activities – Short Form 6a

Please respond to each item by marking one box per row. Not at all		A little bit	Somewhat	Quite a bit		Very much
SRPSAT06r1	I am satisfied with my ability to do things for my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT33_CaPS	I am satisfied with my ability to do things for fun with others.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT34r1	I feel good about my ability to do things for my friends.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT49r1	I am satisfied with my ability to perform my daily routines	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT33r1	I am satisfied with my ability to do things for fun outside my home	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT46_CaPS	I am satisfied with my ability to meet the needs of my friends.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Physical Function – Short Form 10a

Please respond to each question or statement by marking one box per row.	Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFA1 Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC36r1 Does your health now limit you in walking more than a mile (1.6 km)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC37 Does your health now limit you in climbing one flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5 Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA3 Does your health now limit you in bending, kneeling, or	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Cannot do
	stooping?					
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body? ..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC45r1	Are you able to sit on and get up from the toilet?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

APPENDIX I: Collection of Indirect and Nonmedical Direct Costs (Modified COIN)

Subject ID:_____
Date Completed:_____

PRELIMINARY INFORMATION

1. What was your employment status at the time your cancer was diagnosed?

O Working full time

O Working part time

O Homemaker

O Disabled

O Unemployed and seeking work

O Retired

O Student

O Other; specify: _____

2. What best describes your occupation at the time of your cancer diagnosis? If you were not employed, which category best describes your last job?

O Professional, technical (e.g., teacher, lawyer, physician, engineer)

O Manager, administrator or proprietor (e.g., manager, real estate agent, postmasters)

O Clerical and related (e.g., secretary, clerk, mail carrier)

O Sales occupations (e.g., sales person, demonstrator, agent or broker)

O Service occupations (police, cook, hairdresser)

O Skilled crafts, repair work (e.g., carpenter, telephone line worker)

O Equipment or vehicle operator (e.g., driver, brakeman)

O Laborer (e.g., helper, longshoreman, warehouse worker)

O Farmer (owners, managers, operators, tenants)

O Military

O Homemaker

O Not working

O Other; specify:_____

3. Which category best describes your gross/before taxes earnings at the time

Your cancer was diagnosed? (your average income from your job, as opposed to income from interest on investments)

O Less than $10,000

O $10,000---$19,000

O $20,000---$39,000

O $40,000---$59,000

O $60,000---$79,000

O $80,000---$99,000

O $100,000---$150,000

O Over $150,000

4. What type of health insurance did you have at the time of your cancer diagnosis?

O Medicaid

O Medicare

O Disability insurance

O HMO

O Individual health insurance

O Group health insurance

O National health insurance

O VA/military sponsored

O No insurance (self pay)

O No insurance, no means of payment

5. What is your current employment status?

O Currently working full time

O Currently working part time

O Homemaker

O Disabled

O Unemployed and seeking work

O Retired

O Student

O Other; specify: _____

6. If you are not working, when did you stop? _____/_____/_____
N/A (Not Applicable); presently working

OUT---OF---POCKET COSTS

Please indicate the number of times the following services were used OVER THE LAST MONTH related to your cancer care, whether it was covered all or in part by your insurance, and the out of pocket costs to you (including co---payments).

Service used	# of times	Insurance coverage All Part None	Out---of---pocket costs
7. Visiting nursing care			$
8. Home health care			$
9. Physical/occupational therapy			$
10. Transportation (for medical purposes only)			$
11. Parking (for medical purposes only)			$
12. Prescriptive medication			$
13. Over---the---counter medication			$
14. Hospital bills			$
15. Physician bills			$
16. Special food or food supplements			$
17. Supplies (e.g., urinary pads, dressings)			$
18. Equipment (e.g., wheelchair, oxygen)			$
19. Mental health counselors			$
20. Any others?			
O Yes, please specify:			$

1 _____
2 _____
3 _____
4 _____
5 _____

O No

APPENDIX J: Economic Hardship

ID:_____
Date
Completed:_____

Please circle or check one answer that best applies to you.

Financial Strain

	Almost Never	Once in a While	Sometimes	A lot of the time (frequently)	Almost Always
In the next three months, how often do you think that you and your family will experience bad times such as poor housing or not having enough food?	1	2	3	4	5
In the next three months, how often do you expect that you will have to do without the basic things that your family needs?	1	2	3	4	5

Inability to Make Ends Meet	**A great deal of difficulty**	**Quite a bit of difficulty**	**Some difficulty**	**A little difficulty**	**No difficulty at all**
Think back over the past 3 months and tell us how much difficulty you had paying your bills. Would you say you had...	1	2	3	4	5

	More than enough money left	**Some money left**	**Just enough money left**	**Somewhat short of money**	**Very short of money**
Think again over the past 3 months. Generally, at the end of each month did you end up with...	1	2	3	4	5

Not Enough Money for Necessities
Please think about how you
Felt about your family's

economic situation over thee past 3 months. Indicate how much you would agree or disagree with each statement.	**Strongly agree**	**Agree**	**Neutral/mixed**	**Disagree**	**Strongly disagree**
My family had enough money to afford the kind of home we should have.	1	2	3	4	5
We had enough money to afford the kind of clothing ae should have.	1	2	3	4	5
We had enough money to afford the kind of furniture or household appliances we should have.	1	2	3	4	5
We had enough money to afford the kind of car we need.	1	2	3	4	5
We had enough money to afford the kind of food we should have.	1	2	3	4	5
We had enough money to afford the kind of medical care we should have.	1	2	3	4	5
My family had enough money to afford leisure and recreational activities.	1	2	3	4	5

Economic Adjustments/Cutbacks

In the last 3 months, has your family made any of the following adjustments because of financial need?	**Yes**	**No**
	1	**2**
Changed food shopping or eating habits a lot to save money		
Shut down the heat or air conditioning to save money even though it made the house uncomfortable		

Didn’t go to see the doctor or
Dentist when you needed to
Because you had to save money

Fell far behind in paying bills

APPENDIX K: COST (Comprehensive Score for financial Toxicity) Patient –Reported Outcome Measure

	Not at all	A little bit	Somewhat	Quite a bit	Very much
1 I know that I have enough money in savings, retirement, or assets to cover the costs of my treatment.	0	1	2	3	4
2 My out---of---pocket medical expenses are more than I thought they would be.	0	1	2	3	4
3 I worry about the financial problems I will have in the future as a result of my illness or treatment.	0	1	2	3	4
4 I feel I have no choice about the amount of money I spend on care.	0	1	2	3	4
5 I am frustrated that I cannot work or contribute as much as I usually do.	0	1	2	3	4
6 I am satisfied with my current financial situation.	0	1	2	3	4
7 I am able to meet my monthly expenses.	0	1	2	3	4
8 I feel financially stressed.	0	1	2	3	4
9 I am concerned about keeping my job and income, including work at home.	0	1	2	3	4
10 My cancer or treatment has reduced my satisfaction with my present financial situation.	0	1	2	3	4
11 I feel in control of my financial situation.	0	1	2	3	4

Supplementary Table 3. Final 11---item COST measure. Items 1, 6, 7 and 11 should be reversed scored, as higher scores **i**ndicate higher distress.

COST - Financial Toxicity scoring template 28th March 2014

Instructions:*

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the scale, then divide by the number of items answered. This produces the final score.
4. The higher the score, the higher the financial toxicity.

Item Code	Reverse code		Item response		Item Score
1	4	-	_____	=	_____

2	0	+	_____	=	_____
3	0	+	_____	=	_____
4	0	+	_____	=	_____
5	0	+	_____	=	_____
6	4	-	_____	=	_____
7	4	-	_____	=	_____
8	0	+	_____	=	_____
9	0	+	_____	=	_____
10	0	+	_____	=	_____
11	4	-	_____	=	_____

Sum individual item scores: _____
Multiple by 11: _____
Divide by number of items answered: _____ **= COST score**

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on---line at www.facit.org.

APPENDIX L: PHARMACOKINETICS SHEET DAY 28 - OLAPARIB

Phase IIA trial of delayed initiation of olaparib maintenance therapy in platinum sensitive recurrent ovarian cancer

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At approximately Day 28, right before the patient would otherwise take their dose, **~3-4 mL** of peripheral blood will be collected in a purple top tube (e.g. BD vacutainer 367861 plastic 13 x 75 4 mL tube); Invert tube to mix; centrifuge for 10 min at ~1000 x g; aspirate plasma and place into appropriately-labeled microcentrifuge tubes. After processing, store plasma at -70°C or below. *At the time of sample transfer, a copy of this completed PK form must be transferred also.*

Note the times administering of oral dose, in this form; speciifcally the time of previous dose, and the time of the dose immediately after the blood draw.

Olaparib

Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Day ~28	**Administer the olaparib after taking the blood sample**		
Olaparib Dose (mg):_____ twice daily			
Time of previous olaparib dose			**commonly the night prior**
pre/trough blood sample			
Time of olaparib dose immediately after sample			