SUMMARY OF CHANGES – Protocol

For Protocol Amendment # to: A Phase 1 / 2 Study of Olaparib in Combination with Ramucirumab in Metastatic Gastric and Gastroesophageal Junction Adenocarcinoma (10017760)

NCI Protocol #: # 10066
Local Protocol #: 200021407

NCI Version Date:
Protocol Date: 6/2/2022

I. Protocol Changes Requested by CTEP:

#	Section	Comments
1.	Title Page	**The study coordinator, data manager and research coordinator were updated to Christina Wiess.**
2.	Title Page	**The protocol amendment dates were updated on the title page.**
3.	**All**	**The protocol version date was updated in the header.**
4.	Schema	**Reinserted text regarding including chest, abdomen, and pelvis imaging and reducing imaging intervals to 12 week (+/- 7 day) intervals for patients that remain on study for > 6 months. Correct schema picture also reinserted.**
5.	10	**Reinserted row for adverse event evaluation in the study calendar.**
6.	10	**Reinserted text and footnotes regarding tumor measurements and radiologic evaluations.**
7.	Title page	**Reinserted Clinicaltrials.gov identifier.**
8.	TOC	**Updated table of contents.**
9.	9.3.6	**The correlative study section as updated to include language for shipping plasma from Yale University to the NCLN Genomics Laboratory for circulating tumor DNA analysis.**
10.	Appendix D	**The wallet card was updated per CTEP recommendations.**

NCI Protocol #: *10066*

Local Protocol #: *2000021407*

ClinicalTrials.gov Identifier: *NCT030008278*

TITLE: A Phase 1 / 2 Study of Olaparib in Combination with Ramucirumab in Metastatic Gastric and Gastroesophageal Junction Adenocarcinoma (10017760)

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NCI-Supplied Agent(s): Olaparib, NSC 747856
Other Agent(s): Ramucirumab, NSC 749128 commercially available through Eli Lilly

IND #: #[redacted]
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

Original / Version 1 / Version Date 7/25/16
Revision / Version 2 / Version Date 2/15/17
Revision / Version 3 / Version Date 3/31/17
Revision / Version 4 / Version Date 6/26/17
Revision / Version 5 / Version Date 9/12/17
Amendment / Version 6 / Version Date 1/29/18
Amendment / Version 7 / Version Date 4/30/18
Amendment / Version 8 / Version Date 7/25/18
Amendment / Version 9 / Version Date 1/31/19
Amendment / Version 10 / Version Date 3/25/19
(Withdrawn by CTEP)

Amendment / Version 11 / Version Date 5/29/19
Amendment / Version 12 / Version Date 6/2/2022

SCHEMA

This study begins with a phase 1 dose escalation lead-in with olaparib and ramucirumab for eligible patients with metastatic gastric or gastroesophageal junction adenocarcinoma who have previously received at least one line of chemotherapy in the metastatic setting. A 3+3 dose escalation design will be done for olaparib at doses of 200mg BID and 300mg BID (tablet formulation) with standard ramucirumab dosing of 8 mg/kg every 2 weeks. After the recommended phase 2 dose is determined, the phase 2 part of the study will begin. In phase 2, patients will be enrolled and treated with olaparib twice daily and ramucirumab 8 mg/kg every 2 weeks. Response assessment scans will be done every 6 weeks (imaging should include the chest, abdomen and pelvis), and treatment will continue until disease progression or unacceptable toxicity. Patients that remain on treatment for > 6 months may decrease the response assessment scan interval to every 12 weeks (+/- 7 days) at the discretion of the investigator. All patients will undergo a biopsy prior to treatment, which will be used for integrated biomarker analysis with the BROCA-HR panel to assess for the presence of mutations in homologous repair genes. The patients in phase 2 will also undergo an optional repeat biopsy at 16 weeks for correlative analysis including development of a post treatment PDX. Within the BROCA-HR panel we estimate the 17 genes characteristic of homologous repair deficiency (HRD) to be present in 30-40% of our study population. Deleterious mutations in the following genes will be considered a positive result for the BROCA-HR biomarker: ATM, ATR, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, MRE11A, NBN, PALB2, RAD51, RAD51C, RAD51D, RBBP8, SLX4, XRCC2, CDK12. Because we do not know the true distribution of our biomarker, we will proceed with this 40 patient pilot study to help plan a larger study based on both our observed biomarker prevalence and our response rates. If response rates are observed regardless of biomarker status the subsequent study may not be biomarker driven. Based on published data in the COSMIC and TCGA databases we expect the BROCA-HR biomarker to be positive in approximately 35% of cases and we will enroll to 40 patients in phase 2 and proceed as follows:

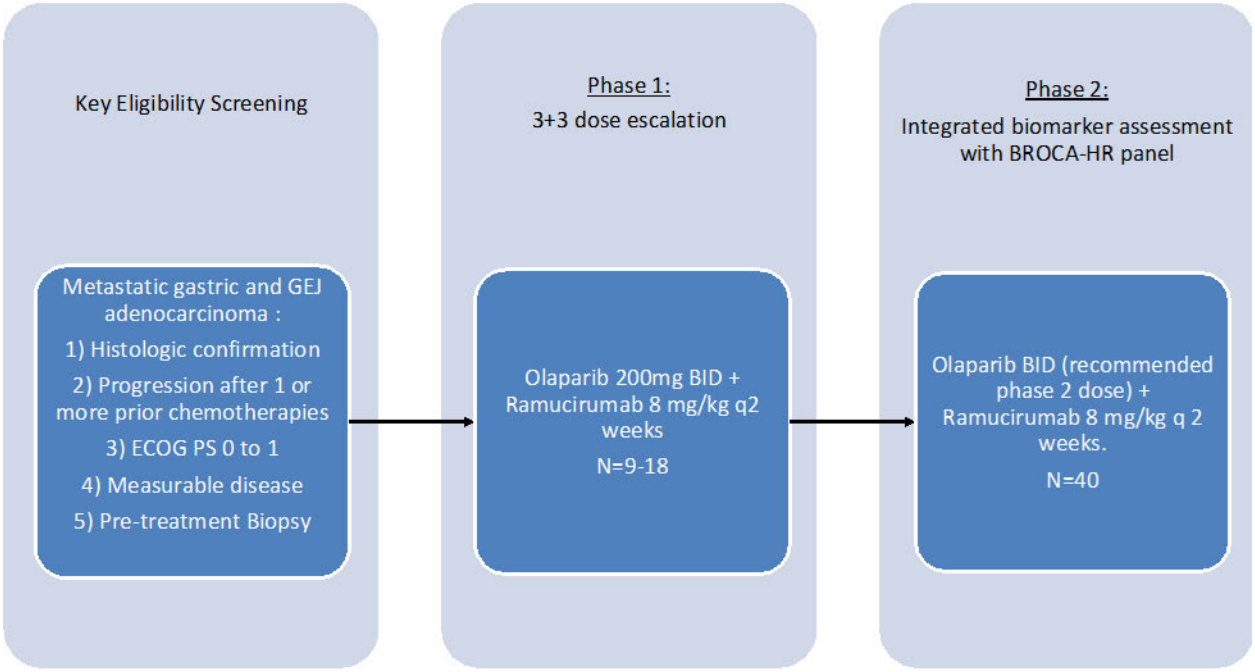
1. If there are 6 or more BROCA-HR+ patients (34 or less BROCA-HR- patients): If there are no responses in BROCA-HR+ patients and no response in BROCA-HR- patients, then it is unlikely we will proceed to a larger study with this combination.
   - For BROCA-HR+ patients: the probability of ≥ 1 responses is > 80% if the true response rate ≥ 25%
   - For BROCA-HR- patients: The probability of ≥ 1 response is > 99% if the true response rate is ≥ 20% and the probability of ≥ 1 response of 80% if the true response rate is ≥ 5%.

2. If there are 6 or more BROCA-HR+ patients (34 or fewer BROCA-HR-): For BROCA-HR- patients, the study will require at least 4 responses for success if we have at least 26 BROCA-HR- patients (65% incidence rate). The probability

of 4 responses is 80% if the true response rate is 20%. The study will require at least 3 responses for success if we have at least 20 BROCA-HR- patients (50% incidence rate) the probability of ≥ 3 responses = 80% if the true response rate = 20%. It is very unlikely the incidence rate of BROCA-HR- will be less than 50%.

3. If there are less than 6 BROCA-HR+ patients (35 or more BROCA-HR- patients): If no responses are observed in either cohort, then it is unlikely we will proceed to a larger study with this combination. The probability of ≥ 6 BROCA-HR+ patients is > 85% if the true incidence of BROCA-HR+ is ≥ 20%. The probability of ≥ 6 BROCA-HR+ patients is > 99% if the true incidence rate of BROCA-HR+ is ≥ 35%.

Based upon the results in the above scenarios we will discuss with CTEP on the plan to proceed to a larger study.



Dose Escalation Schedule			
Dose Level	**Dose***		
	Olaparib	**Ramucirumab**	***N/A***

	(mg)	***(mg/kg)***	
-2	100 mg, twice daily	8 mg/kg every 2 weeks, intravenous	
-1	150 mg, twice daily	8 mg/kg every 2 weeks, intravenous	
1 (starting dose)	200 mg twice daily, orally	8mg/kg every 2 weeks, intravenous	
2	300 mg twice daily, orally	8mg/kg every 2 weeks, intravenous	

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1. OBJECTIVES

1.1 Primary Objectives

1.12 Phase 1 Primary Objective:
To determine the safe dose of olaparib with ramucirumab, but not to exceed olaparib dose of 300mg twice daily (tablet formulation).

1.13 Phase 2 Primary Objective:
To determine the efficacy of olaparib plus ramucirumab as measured by the objective response rates (ORR) stratified by BROCA-HR biomarker status.

1.2 Secondary Objectives
- To estimate median progression-free survival (PFS) stratified by BROCA-HR biomarker status.
- To estimate median overall survival (OS) stratified by BROCA-HR biomarker status.
- To measure the prevalence of the BROCA-HR biomarker in our study population.
- To determine toxicity of olaparib and ramucirumab combination.

1.3 Exploratory Objectives
- To assess the correlation between the signature 3 status and mutations in BROCA-HR panel.
- To evaluate the association between findings from BROCA-HR panel with response to therapy.
- To evaluate the association between findings from BROCA-HR panel and signature 3 results with response to therapy.
- To determine results of immunoassay for poly-ADP-ribosylated (PAR) substrates in tumor tissue.
- To create a PDX model to study DNA repair in gastric tumors treated with PARP inhibitors (PARPi) from both pre-treatment biopsy and repeat biopsy after 16 weeks of treatment.
- Development of a novel genomic assay for BRCAness
- Defining T cell receptor diversity of gastric cancer patients +/- BRCAness
- Biobank additional tumor tissue for future genomic analysis.
- Biobank peripheral blood for future genomic analysis and assessment of circulating tumor DNA.

2. BACKGROUND

2.1 Gastric and Gastroesophageal Adenocarcinoma

Despite decreased incidence, gastric cancer remains a significant public health problem in the state of Connecticut, US, and globally. Moreover, the incidence of GEJ-centered adenocarcinomas has increased dramatically in Western countries over the past four decades. It is estimated that were will be 26,370 new cases of gastric cancer, and 16,910 new cases of

esophageal cancer, the majority of which are GEJ–centered adenocarcinomas, in the United Stats in 2016 [1]. Global gastric cancer incidence has declined with improved sanitation, food preparation and infection control, but the most recent global incidence remains high with 951,600 cases in 2012 [2]. The five-year survival rate of gastroesophageal adenocarcinoma is <30% for all stages and < 4% for metastatic disease [3, 4]. It's estimated that were will be 310 deaths attributed to gastroesophageal cancer for Connecticut in 2016 [5]. Thus, gastric and GEJ adenocarcinomas remain highly lethal with early propensity for metastatic spread, and despite new therapies, improvement in survival has been modest [4].

National Comprehensive Cancer Network (NCCN) guidelines for metastatic gastroesophageal adenocarcinoma recommend a platinum containing doublet or triplet in the first line setting, but median survival is less than 1 year [6]. Approved second-line regimens include ramucirumab as single agent or in combination with paclitaxel [7, 8]. Targeted therapy for HER2 positive disease with trastuzumab has been effective [9], but the role for other targeted agents remains unclear. Olaparib in combination with paclitaxel has shown mixed results in gastric cancers expressing low levels of the ataxia telangiectasia (ATM) protein and further study is ongoing [10]. Low levels of ATM protein are thought to be a sign of defective double stranded DNA repair mechanisms through interaction with BRCA [10]. Gastric cancer cell lines have demonstrated sensitivity to olaparib, which is even more pronounced with low levels of ATM expression [11].

Defective DNA repair is a widely known mechanism for cancer development. BRCA mutations result in defective DNA repair by causing defects within error-free homology-directed double strand break repair. Cells must then rely on the more error prone non-homologous DNA repair, which results in increased mutational burden within cells and predisposes to breast, ovarian, and pancreatic cancer. While the association between BRCA mutation and gastric cancer is weaker than the association with breast and ovarian cancer, recent data reveals that evidence of homologous recombination deficiency (HRD) may be present in up to 12% of non-BRCA mutated gastric cancers as determined by a molecular signature for HRD. This observation is discussed further in Correlative Studies Background, section 2.5.2 [12].

Additional evidence supporting defective homologous repair in the pathogenesis of gastric cancer relates to mutations in reported in the DNA repair gene ATM. Mutations in ATM have been reported in 11% of gastric cancers, and found to be expressed at low levels in 14% of patients in a prospective study [10, 13, 14]. The BROCA-HR mutation panel developed by Dr. Swisher at the University of Washington is a gene panel that has been validated and is available to assess for the presence of mutations in 84 DNA repair genes. This panel contains 17 DNA repair genes with actionable mutations, including ATM and BRCA. Mutations within the BROCA-HR panel have been reported in more than 40% of gastric cancers reported in the cosmic database, and details regarding the panel are discussed further in the Correlative Studies Background, section 2.5.1 [15, 16]. The use of the BROCA-HR panel and the use of mutational signatures both present opportunities as biomarkers to identify tumors with defective homologous repair that may be more susceptible to the combination of ramucirumab and olaparib. The rationale for this combination is further described in section 2.4. A separate test, the Myriad HRD assay, measures homologous recombination in tumor cells. Homologous repair is measured by three components: loss of herozygosity, large-scale state transitions, and telomeric allelic imbalance [17]. The Myriad assay is currently under review for validation for

ovarian and breast cancer, but also presents an opportunity for use as a biomarker for defective homologous repair in gastric patients [17, 18].

2.2 CTEP IND Agent(s)

2.2.1 ***Olaparib (AZD 2281)***

Olaparib (AZD2281, KU-0059436) is a potent oral inhibitor of polyadenosine 5'diphosphoribose polymerase (PARP). PARP inhibition is a novel approach to targeting tumors that have homologous recombination DNA repair pathway deficiencies. In HRD tumors, single agent treatment with olaparib can lead to tumor regression by a process known as synthetic lethality- a result of the accumulation of un-repaired DNA double-strand breaks and an unsupportable increase in genomic instability. In synthetic lethality, neither the deficiency in homologous repair nor PARP inhibition is cytotoxic by itself, but the combination of both leads to cell death.

Olaparib is the first PARP inhibitor approved by regulatory agencies for clinical indication. In the US, the FDA has approved olaparib as monotherapy for patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) in patients with advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Additionally, the European Medicines Agency (EMA) approved olaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

The majority of completed studies were performed with the capsule formulation of olaparib. However since 2012/2013 most new studies, including the phase III registration studies, are being performed with the tablet formulation which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule.

Mechanism of Action
The mechanism of action for olaparib activity has been proposed to involve the trapping of inactivated PARP onto the single-strand breaks preventing their repair and generating a potential block for cellular DNA replication [19, 20]. An important consequence of this is that processing of trapped PARP-DNA complexes and/or the stalling of replication forks, or collapsing of replication forks leads to the generation of more serious DNA double stranded breaks [19, 20]. Under normal circumstances these double stranded breaks would be repaired by processes that involve ATM and additional homologous recombination DNA repair proteins such as RAD51, BRCA1, and BRCA2 (Olaparib IB v. 14). However, when homologous repair is not functioning cells must rely on the more error prone base-excision repair system, which requires PARP function. Homologous repair dysfunction sensitizes cells to PARP inhibition leading to further chromosomal instability, cell cycle arrest and apoptosis [21]. In cases where DNA repair defects may not result in the same level of sensitivity as BRCA mutations single agent olaparib may not be sufficient to induce cell kill through synthetic lethality. However, it may still be possible to induce tumor cell death through combinations with ionizing radiation or chemotherapies that either increases DNA damage accumulation or mitotic stress. Pre-clinical studies support these

findings, showing that other BRCA mutant, but not wild-type, human cell lines are highly sensitive to olaparib [22].

Nonclinical Pharmacology and Efficacy
Olaparib was developed as a PARP inhibitor from a targeted screening program of pharmacophores with the aim of enhancing killing actions of certain existing cancer chemotherapies such as topoisomerase I inhibitors and alkylating agents. Olaparib is an agent that has potential both as monotherapy as well as in combination with other cancer treatments [22].

Multiple tumor cell lines have been investigated using colony formation assays for sensitivity to PARP inhibition with olaparib as a single agent. These cell lines have shown wide-ranging cellular activity from low nM to 10μM. The effective concentration for inhibiting cellular PARP activity in cancer cells by >90% is approximately 30 nM to 100 nM olaparib in several human tumor cell lines including ovarian A2780, breast MCF-7, and colorectal SW620. These concentrations led to significant ablation of PARP activity (based on the inhibition of PAR formation), with maximal PARP-1 inhibition occurring at around 100 nM. Consistent with this, maximal potentiation of an appropriate DNA SSB-inducing chemotoxic agent (MMS) was also seen *in vitro* at 100 nM, which equates to 43.4 ng/mL.

Following single oral doses, absorption was rapid (maximum plasma concentration Cmax <2 hours in mice, rats and dogs) while bioavailability was <60% in male and female mice, <20% in male and female rats and ~79% in male dogs (Olaparib IB v. 14). Low oral bioavailability in rats may have been due to poor absorption or rapid first pass metabolism. Distribution of olaparib is in the gastrointestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Further investigations are still ongoing. Excretion is primarily via the feces (65% to 75%) and, to a lesser extent, the urine (20% to 30%).

Investigations in human *in vitro* systems indicated metabolism of olaparib was CYP mediated and that CYP3A4 and 3A5 were the dominant metabolic enzymes (Olaparib IB v. 14). Similar studies indicated flavin mono-oxygenase-3 was not able to metabolize olaparib. For *in vitro* direct inhibition assays, olaparib (0.1 to 500 μM) was a weak inhibitor of CYP3A (IC_{50} 119 μM). Olaparib (0.1 to 100 μM) was also tested against CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1. At <100 μM olaparib, no significant direct inhibitor effect on CYPs 1A2, 2A6, 2B6, 2C8, 2D6 or 2E1 was observed although more limited inhibition of CYP2C9 (22%) and CYP2C19 (26%) was observed. Regulatory guidance suggested clinically meaningful drug interaction due to olaparib directly inhibiting hepatic and GI tract CYP3A4/5 cannot be excluded. In time dependent inhibition assays, olaparib had only very minor effects against CYP3A and no effect against other CYPs.

In studies using Madin-Darby Canine Kidney (MDCK) II cells transfected with multidrug resistance 1 (MDR1; Pgp), BCRP or MRP-2 drug efflux transporters, olaparib was shown to be a substrate of MDR1 but not BCRP or MRP-2 (Olaparib IB v. 14). Olaparib's ability to inhibit MDR1, BCRP, and MRP-2 was also investigated. MDR1 and BCRP were expressed in MDCK II cells while MRP-2 was prepared in isolated membrane vesicles. Olaparib was shown to inhibit MDR1 (IC_{50} 76 μM) and very weakly inhibit BCRP. Olaparib did not inhibit MRP-2. The

possibility for inhibition of hepatic uptake transporters OATP1B1, OATP1B3, OCT1 or NTCP was investigated. Olaparib was an inhibitor of OTAp1B1 and the IC_{50} (20.3 μM and 27.1 μM) was dependent on the substrate used. Olaparib was an inhibitor of OCT1 (IC_{50} 37.9 μM), it caused no significant inhibition of OATP1B3 and was a very weak inhibitor of NTCP (IC_{50} >100 μM) (Olaparib Investigator's Brochure, 2015).

Nonclinical Toxicology
Non-clinical safety evaluation studies conducted with olaparib include single dose oral and iv studies in mice and rats, repeat dosing oral studies of up to 1 months duration in mice, pivotal repeat dosing studies of up to 6 months duration in rats and dogs, a battery of in vitro and in vivo genetic toxicity studies and reproductive toxicology studies in rats, which are summarized in section 4.3 (toxicology) of the Olaparib IB v. 14. There were no noted effects on the cardiovascular or respiratory parameters of an anesthesized dog or any behavioral, autonomic, or motor effects in the rat. Toxicology studies indicate that the target organ of toxicity is the bone marrow. *Ex vivo* work has confirmed that olaparib is also active against human marrow. The cytotoxic effect becomes evident at a higher concentration than required to fully ablate PARP activity. 28-day dog and rat studies demonstrate a reversible myelotoxic effect that is mild to moderate. Platelets are first affected, followed by white blood cells. In 26-week repeat-dose studies in rats, doses were well tolerated in male rats, with hematological effects and increased spleen weights observed at all dosages. In female rats, doses of 15 mg/kg/day resulted in significant reduction in body weight. Hematological effects and increased spleen weights were again observed at all dosages. The difference between sexes was considered to be due to the fact that females had greater plasma exposure levels than males. In 26-week repeat-dose studies in dogs, olaparib was well tolerated. Hematological changes were observed, characterized by pancytopenia.

Clinical Pharmacology – Single-dose Tablet Data (Olaparib IB v. 14)
Following administration of single oral doses of the tablet formulation at doses of 25, 50 and 250 mg (n=6 per cohort), absorption was rapid and slightly more rapid than the capsule dose. The peak plasma concentration was typically achieved at 1.5 hours. Following the peak, plasma concentrations declined in a biphasic manner with an average terminal elimination $t_{1/2}$ of 12.2 hours (Sd 5.31 hours) and 13.02 hours (Sd 4.16 hours). The Gmean apparent oral plasma clearance was approximately 7.95 L/h and 6.36 L/h. The volume of distribution was greater than total body water indicating that olaparib was distributed into the tissues, 146.2 L and 112.1 L. The observed variability in exposure was moderate to high, the Gmean %CV for AUC and Cmax following 300 mg single dose olaparib ranged from 24.3% to 67.4%.

The relative bioavailabilities of the tablet formulation (compared to capsule) at the 3 dose levels studied are shown in Table 10 in the Olaparib Investigator's Brochure, 2015. At the 2 lower tablet doses (25 and 50 mg), following normalization for dose, although the Cmax achieved after dosing with the tablet formulation tended to be higher than that with the capsule, the AUC values for the 2 formulations were actually very similar. However, at the highest tablet dose (250 mg), the exposure delivered by the tablet formulation (both dose-normalized Cmax and AUC) was higher than that delivered by the capsule. The tablet and the capsule formulations cannot therefore be considered to be bioequivalent.

Safety Profile: As of 15 December 2016, approximately 6558 patients are estimated to have received olaparib in the clinical programme including AstraZeneca-sponsored studies (3923 patients), a MAP (676 patients), ISSs and collaborative group studies (1959 patients). An estimated 4475 patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumors are estimated to have received treatment with olaparib in AstraZeneca-sponsored, interventional studies (3799 patients) and the MAP (676 patients). Since 2012/2013, most new clinical studies have utilized the tablet formulation which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. Of the 4475 patients, 2109 received the capsule formulation, 2341 received the tablet formulation, and 25 received both capsule and tablet. In the AstraZeneca-sponsored, interventional studies, olaparib was given either as monotherapy (2618 patients) or in combination with chemotherapy or other anti-cancer agents, including studies where patients received monotherapy and combination therapy sequentially (n=1181).

Data from the available pre-clinical studies and subsequent clinical development programme demonstrate that olaparib appears to be active and generally well tolerated in patients with solid tumours including those with BRCA mutated cancers. In ovarian cancer, responses have been seen in all patient groups, including platinum resistant and refractory cancer.

From the available data to date in patients with advanced cancer, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure.

Adverse laboratory findings and/or clinical diagnoses considered to be associated with administration of olaparib monotherapy include hematological effects (anemia, neutropenia, lymphopenia, thrombocytopenia, MCV elevation and increase in blood creatinine), nausea and vomiting, decreased appetite, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysguesia, fatigue (including asthenia), headache and dizziness. Most of these events were generally mild or moderate in intensity.

In a relatively small number of patients, pneumonitis, MDS/AML and new primary malignancies have been observed. Evidence from across the development programme for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events. There are important potential risks for olaparib and are being kept under close surveillance.

Data from studies of olaparib in combination with various chemotherapy agents indicate an increase in bone marrow toxicity (anemia, neutropenia, thrombocytopenia) greater than expected if the agents had been administered alone. The effects are generally transient but treatment delays are common and alternative administration schedules/toxicity management processes are currently being evaluated within some of these studies. When this type of toxicity has occurred it has been managed by routine clinical practice including dose delays, dose reductions, intermittent dosing and/or the use of supportive care measures, including G-CSF. Currently, all ongoing olaparib combination studies are being closely monitored for myelotoxicity. Results of a Phase II study in combination with carboplatin/paclitaxel (Study D0810C0041) showed that addition of olaparib to carboplatin AUC 4 + paclitaxel in the chemotherapy phase had a generally similar tolerability profile to carboplatin AUC 6 + paclitaxel. The regimen of olaparib

capsule 200 mg bd for 10 days out of 21, with carboplatin AUC 4 + paclitaxel had an acceptable and manageable tolerability profile in patients with recurrent serous ovarian cancer. Olaparib tolerability during the monotherapy maintenance phase was consistent with the previously known safety and tolerability profile. In Study D0810C00039 and Study 081BC00004, olaparib 100 mg tablet bd in combination with weekly paclitaxel 80 mg/m^2 was well tolerated, with no new unexpected safety findings. In both studies, the incidence of neutropenia was higher for the olaparib combination arm and this contributed to higher rates of dose modifications for patients on olaparib compared to placebo. In Study D081BC00004, there was also a higher incidence of anemia on the olaparib + paclitaxel combination arm than the placebo + paclitaxel arm and more dose interruptions, reductions and discontinuations.

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

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

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

Laboratory toxicities:
From the completed studies, there are no safety concerns noted for the renal or hepatic parameters measured and no clinically significant changes of concern relating to coagulation parameters. Changes observed in the hematological parameters (decreased hemoglobin, neutrophils, thrombocytes and lymphocytes) are known to be associated with olaparib monotherapy and/or can be explained by co-existing conditions/previous chemotherapy. Mean

corpuscular volume increases have also been observed with olaparib. The clinical significance of this laboratory finding is unknown. Data from Phase 1 and Phase 2 studies of olaparib in combination with various chemotherapy agents indicate an increase in neutropenia, thrombocytopenia, and anemia compared to giving these agents alone. These findings are consistent with pre-clinical findings and are reflected in the more severe hematological events i.e., CTCAE Grade 4 neutropenia, febrile neutropenia and thrombocytopenia being reported as SAEs.

Mild elevations in creatinine with no apparent sequelae have been observed in the absence of an elevation in urea or blood urea nitrogen or a reported abnormality on urinalysis. The clinical significance of these mild elevations in creatinine is unknown but inhibition of organic cation-transporter-2 by olaparib is considered a plausible mechanistic explanation.

Clinical Efficacy:

The regulatory approvals of olaparib were based on study D0810C00019. This was a Phase 2, randomized, double-blind, multicenter study to assess the efficacy of olaparib (capsule formulation) in the treatment of patients with platinum sensitive serous ovarian cancer, following treatment with 2 or more platinum containing regimens [23]. Patients that responded to platinum based chemotherapy were randomly assigned to maintenance therapy with either placebo or olaparib at a dose of 400mg twice daily. The primary endpoint was PFS according to the RECIST guidelines. Of the 265 patients randomized into the study, all olaparib (136) and 128/129 placebo patients received study treatment. PFS was significantly longer with olaparib than with placebo (median, 8.4 months vs. 4.8 months from randomization on completion of chemotherapy; hazard ratio for progression or death, 0.35; 95% confidence interval [CI], 0.25 to 0.49; $P<0.001$). Subgroup analyses of PFS showed that, regardless of subgroup, patients in the olaparib group had a lower risk of progression. The investigators concluded that olaparib as maintenance treatment significantly improved PFS among patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer. Interim analysis showed no overall survival benefit. The toxicity profile of olaparib in this population was consistent with that in previous studies.

Fong et al reported the result of a phase 1 study in a study population enriched in carriers of a BRCA1 or BRCA2 mutation [24].The investigators enrolled and treated 60 patients; 22 were carriers of a BRCA1 or BRCA2 mutation and 1 had a strong family history of BRCA-associated cancer but declined to undergo mutational testing. The olaparib dose and schedule were increased from 10 mg daily for 2 of every 3 weeks to 600 mg twice daily continuously. Reversible dose-limiting toxicity was seen in one of eight patients receiving 400 mg twice daily (grade 3 mood alteration and fatigue) and two of five patients receiving 600 mg twice daily (grade 4 thrombocytopenia and grade 3 somnolence). This led to enrollment of another cohort, consisting only of carriers of a BRCA1 or BRCA2 mutation, to receive olaparib at a dose of 200 mg twice daily. Other adverse effects included mild gastrointestinal symptoms. There was no obvious increase in adverse effects seen in the mutation carriers. Pharmacokinetic data indicated rapid absorption and elimination; pharmacodynamic studies confirmed PARP inhibition in surrogate samples (of peripheral-blood mononuclear cells and plucked eyebrow-hair follicles) and tumor tissue. Objective antitumor activity was reported only in mutation carriers, all of whom had ovarian, breast, or prostate cancer and had received multiple treatment regimens.

In an expansion phase in BRCA-deficient ovarian cancer at a dose of olaparib 200 mg BID, fifty patients were treated, including 48 with BRCA-deficient germline mutations and two patients of unknown status or significance. Twenty (40%) patients achieved complete response (CR) or partial response (PR) by RECIST and/or GCIG-CA125 criteria. An additional three patients experienced stable disease (SD) for more than four cycles [25]. A multicenter phase 2 study enrolled two sequential cohorts of women with known germline BRCA1 or BRCA2 mutations and recurrent advanced ovarian cancer to receive olaparib continuously at a dose of 400 mg BID (Cohort 1) or 100 mg BID (Cohort 2) [26]. Responses were observed in 33% (11 of 33) patients enrolled in the 400mg BID cohort and 13% (3 of 24) patients enrolled in the 100 mg BID cohort. A phase 2 study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer showed ORR of 41% in ovarian patients with BRCA1 or BRCA2 mutations and 24% without mutations and no confirmed responses in patients with breast cancer [27].

Kaufman et al reported the results from the phase 2 study of olaparib monotherapy in patients with advanced solid cancer and germline *BRCA1/2* mutation [28]. Olaparib was given 400mg twice a day and the primary endpoint was tumor response rate. A total of 298 patients received treatment and were evaluable. The tumor response rate was 26.2% (78 of 298; 95% CI, 21.3 to 31.6) overall and 31.1% (60 of 193; 95% CI, 24.6 to 38.1), 12.9% (eight of 62; 95% CI, 5.7 to 23.9), 21.7% (five of 23; 95% CI, 7.5 to 43.7), and 50.0% (four of eight; 95% CI, 15.7 to 84.3) in ovarian, breast, pancreatic, and prostate cancers, respectively. Stable disease ≥ 8 weeks was observed in 42% of patients (95% CI, 36.0 to 47.4), including 40% (95% CI, 33.4 to 47.7), 47% (95% CI, 34.0 to 59.9), 35% (95% CI, 16.4 to 57.3), and 25% (95% CI, 3.2 to 65.1) of those with ovarian, breast, pancreatic, or prostate cancer, respectively.

Lee and Kohn and colleagues have examined olaparib with carboplatin in two schedules in BRCA1/2 mutation carriers with breast and/or ovarian cancer and women with high grade serous ovarian cancers[29]. They also observed clinical activity with over 80% of ovarian cancer patients attaining either SD or PR lasting up to 18+ months. Additional phase 1 and 2 trials in both BRCA-deficient and BRCA-competent ovarian cancer are currently ongoing.

2.3 Other Agent: Ramucirumab (Cryamza)

Pathways that mediate angiogenesis are considered important targets in cancer drug development and drugs that target this pathway have been correlated with multiple outcomes. Vascular endothelial growth factors (VEGFs; including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor) have emerged as key regulators of angiogenesis and the expression of VEGFs has been correlated with poor prognosis in several solid tumor types, including gastric adenocarcinoma.

A comprehensive clinical development program to assess ramucirumab in the treatment of solid tumor malignancies was initiated following Phase 1 studies evaluating dose, schedule, and toxicity. The clinical development has focused on tumors where VEGF ligands (including VEGF-A) and VEGF-R2 are overexpressed and where the unmet medical need is high [30, 31].

Mechanism of Action

Ramucirumab is a human receptor-targeted antibody that specifically binds VEGF Receptor 2 (VEGF-R2). The binding of ramucirumab to VEGF-R2 prevents its interaction with activating ligands, VEGF-A, VEGF-C, and VEGF-D [31, 32]. As a result, ramucirumab inhibits ligand-stimulated activation of VEGF-R2, thereby inhibiting ligand-induced proliferation, downstream signaling components including Erk1/Erk2, and migration of human endothelial cells [33, 34]. Preclinical data for DC101, a neutralizing rat anti-mouse mAB specific for murine VEGF-R2, demonstrate antitumor activity in multiple tumor models.

Nonclinical Pharmacology, Efficacy and Toxicology (Ramucirumab Investigator's Brochure 2014)

The pharmacokinetics (PK) and toxicokinetics (TK) of ramucirumab were determined in cynomolgus monkeys. The PK behavior of ramucirumab in monkeys was typical of a monoclonal antibody. The PK was nonlinear and showed antibody accumulation with repeated doses. The formation of antidrug antibodies (ADA) was assessed in all primate studies, and generally indicated the presence of ADA in individual animals; however, the predictive value of this finding for the occurrence of immunogenicity in humans is unclear. Formal studies to characterize the disposition, excretion, and metabolism of ramucirumab have not been conducted. As a monoclonal antibody, ramucirumab will be largely confined to the extracellular space and elimination is primarily by catabolism of the antibody.

PK and TK of ramucirumab in cynomolgus monkeys was obtained in 5 and 39 week repeat-dose toxicology studies. Animals were administered IV doses of 0, 4, 12, or 40 mg/kg ramucirumab DP weekly and blood samples for ramucirumab concentration analysis in serum were obtained after the first dose.

Non-compartmental analysis of the contentration-vs-time data from the monkey toxicology studies indicated that the PK behavior of ramucirumab was non-linear over the 4-50 mg/kg dose range. Ramucirumab half-life increased and clearance decreased with increasing dose. The steady-state volume of distribution was approximately equal to the vascular space at each dose level. Mean ramucirumab AUC in the 50mg/kg group increased between the first and 39^{th} doses, indicating that drug accumulation occurred. Antibodies against ramucirumab were detected in the 4, 12, and 40 mg/kg dose groups in the 5 week study and in the 5, 16 mg/kg dose groups in the 39 week study. The PK behavior of ramucirumab in monkeys is thus nonlinear and typical of a monoclonal antibody.

The toxicity of IV ramucirumab was evaluated in monkeys that received 4 doses over 5 weeks, or weekly doses for up to 39 weeks. The effect of ramucirumab was also assessed in an incisional model of wound healing after a single IV dose, and no impairment in wound healing was observed. Focal muscle fiber degeneration and mononuclear cell infiltration were seen in skeletal muscle in ramucirumab treated animals only, but were concluded to not be treatment related due to the focal nature of lesions and low incidence in females. No ramucirumab related adverse events were evident in the routine toxicological assessments. Treatment of monkeys with ramucirumab for 39 weeks resulted in renal toxicity at doses of 16 and 50 mg/kg and thickening

and osteochondropathy of the epiphyseal growth plate noted at 5 mg/kg and above. Thus a no observable adverse effect level for ramucirumab was not established when administered to monkeys once a week for 39 weeks.

Nonclinical in vitro pharmacodynamics studies demonstrated that ramucirumab possesses high affinity for VEGF receptor 2 and that picomolar concentrations of the antibody can inhibit binding of VEGF in vitro. Thus ramucirumab potently inhibits VEGF-mediated VEFR2 activating, signaling, and biologic effects in endothelial cells. These responses include cell migration, proliferation, and survival. Pharmacological proof-of principle experiments that validated targeting VEGFR2 as an antiangiogenic strategy depended on the use of a surrogate antibody, DC101.

The preclinical pharmacodynamics data demonstrated that ramucirumab binds specifically and with high affinity to human VEGFR2, and not to murine VEGFR2 or the related human VEGF receptors, VEGF receptor 1 and VEGF Receptor 3. Additionally, ramucirumab is capable of inhibiting the relevant in vitro biological consequences of VEGF stimulated activation of VEGFR2. The antiangiogenic and antitumor effects observed in mice treated with DC101 provide the basis to anticipate potent antiangiogenic effects of ramucirumab in human cancers.

Clinical Pharmacology

Serum ramucirumab concentrations were determined using either an original bioanalytical assay or a modified bioanalytical assay. The original PK assay was modified and validated to meet the industry bioanalytical assay standards. Only data using the modified assay are considered the primary source for ramucirumab PK characterization and are presented.

For gastric cancer, trough concentrations (or minimum concentrations) were collected in both the Phase 2 and 3 studies for the REGARD and RAINBOW clinical trials. Using the dosing regimen of ramucirumab 8 mg/kg every 2 weeks the observed minimum concentration values were similar between both REGARD and RAINBOW. The mean observed trough values were approximately 50 μg/mL and approximately 60 to 70 μg/mL before the fourth and seventh doses, respectively.

In a pooled analysis of 11 studies involving 1639 patients across multiple cancers revealed the volume of distribution at steady state (Vm) and terminal half life were 0.0147 L/h (30.0%) and 5.4L (15.0%) and 14 days (20.0%) respectively. Results from this pooled analysis indicate that the PK of ramucirumab following 8 and 10 mg/kg dose administrations were linear and time independent. Covariate analysis indicate that ramucirumab is not affected by body weight, sex, age, serum albumin, race, hepatic status, and renal function.

Two dedicated studies were conduced to assess the effect of concomitant ramucirumab administration on the PK of paclitaxel and docetaxel. In study 14T-IE-JVCA was demonstrated that concomitant administration of ramucirumab had no effect on the dose normalized AUC and Cmax of paclitaxel. Similarly in study 14T-IE-JVCB dose normalized AUC and Cmax of irinotecan and SN-38 in cycle 2 were similar to those when FOLFIRI was administered alone in cycle 1, which suggests that concominant administration of ramucirumab is unlikely to impact

the PK of irinotecan and its active metabolite SN-39. In study 14T-IE-JVCC the dose-normalized AUC and Cmax of docetaxel were similar whether docetaxel was administered with or without ramucirumab, which suggests that concominant administration of ramucirumab is unlikely to impact the PK of docetaxel.

Safety Profile

Weekly doses of ramucirumab ranging from 2 to 16mg/kg were evaluated in the Phase 1 study JVBM. An MTD for weekly dosing was identified as 13 mg/kg. Every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20mg/kg) dose regimens were evaluated in an additional dose ranging study (Study JVBN). All dose regimens in study JVBN were well tolerated and no MTD was identified in this study.

REGARD demonstrated a well-tolerated safety profile in the gastric cancer monotherapy setting. Due to the low incidence of hypertension and neutropenia, no safety-exposure relationship was identified.

In RAINBOW, the overall safety profile was also considered management, although increasing ramucirumab exposure was correlated with increased incidence of Grade 3 or greater hypertension, neutropenia, and leukopenia. Of note, there were no Grade 4 or 5 hypertension events in RAINBOW. Hypertension was managed primarily by the use of standard antihypertensive medication, and the association of neutropenia with ramicurmab exposure does not appear to translate to an increased risk of febrile neutropenia with higher ramucirmab exposure.

Laboratory Toxicities

In study 14T-MC-JVBT(ramucirumab and FOLFOX) the overall safety profile for ramucirumab revealed the most common Grade ≥3 AE reported regardless of causality was:

- **a.** Neutropenia 22 patients (26.8%) in ramucirumab arm vs 29 patients (36.3%) in placebo arm
- **b.** Fatigue 15 patients (18.3%) in ramucirumab arm vs 12 patients (15.0%) in placebo arm
- **c.** Neuropathy 7 patients (8.5%) in ramucirumab arm vs 9 patients (11.3%) in placebo arm
  22 patients (26.8%) in ramucirumab arm vs 29 patients (36.3%) in placebo arm

In study 14T-IE-JVBD (REGARD) the most common Grade ≥3 was:

- **d.** Hypertension 7.6% in ramucirumab arm vs 2.6% in placebo arm

In study 14T-IE-JVBE (RAINBOW) the most common Grade ≥3 was:

- **e.** Fatigue 11.9% in ramucirumab arm vs 5.5% in placebo arm
- **f.** Neutropenia 40.7% in ramucirumab arm vs 18.8% in placebo arm
- **g.** Leukopenia 17.4%% in ramucirumab arm vs 6.7% in placebo arm
- **h.** Hypertension 14.1% in ramucirumab arm vs 2.4% in placebo arm

Clinical Efficacy

Several factors provided rationale for further clinical development of ramucirumab in gastric cancer; these include contribution of angiogenesis to cancer pathogenesis, and preclinical evaluations of the rat antibody to murine VEGF-R2, DC101. Ramucirumab does not cross react with the murine VEGF-R2, and for this reason DC101 was used in murine models, and preliminary evidence of potential activity of other antiangiogenic agents in gastric cancer [35, 36].

Clinical activity was seen early in the development of ramucirumab. In Phase 1 studies, ramucirumab was generally well tolerated and exhibited preliminary evidence of anti-tumor activity in patients with solid tumors. The maximum tolerated dose (MTD) of ramucirumab was identified to be 13 mg/kg when given once weekly in the phase 1 dose-escalation study, Study 14T-IE-JVBM (JVBM). Preliminary activity was observed across a range of doses, including the 2-mg/kg weekly dose. Every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20 mg/kg) dose regimens were evaluated in an additional dose-ranging study, 14T-IE-JVBN (JVBN). No MTD was identified for every-2-week or every-3-week dosing; all dose regimens were well tolerated, and preliminary evidence of clinical efficacy was observed across a range of dose/schedule cohorts [7].

Two dose regiments, 8 mg/kg every 2 weeks and 10 mg/kg were selected in the subsequent phase 2 and phase 3 studies. The ramucirumab dose of 8 mg/kg every 2 weeks has demonstrated a statistically significant and clinically meaningful benefit in OS in the phase 3 REGARD study: ramucirumab plus BSC vs placebo plus BSC with advanced gastric cancer. Median OS was 5.2 months in the ramucirumab arm versus 3.8 months in the placebo arm (Hazard ratio = 0.776, 95% confidence interval [CI]: 0.603, 0.998; p=0.47). Ramucirumab was well tolerated in this patient population with similar rates for most adverse events (AEs) between the ramucirumab and placebo arms. Rates of hypertension were higher in the ramucirumab arm than in the placebo arm (38 [16%] vs 9 [8%]), whereas rates of other AEs were mostly similar between arms (223 [94%] vs 101 [88%]). Five (2%) deaths in the ramucirumab arm and 2 (2%) in the placebo arm were considered to be related to study drug. Based on this benefit, ramucirumab monotherapy was approved as a second line treatment for metastatic gastric cancer.

The approval of ramucirumab in combination with paclitaxel in patients with advanced gastric or GEJ cancer whose disease has progressed after prior platinum/fluoropyrimidine-based chemotherapy was based on the randomized RAINBOW Phase 3 study [8]. The primary endpoint of OS was met; median OS was 9.63 months on the ramucirumab plus paclitaxel arm compared with 7.36 on the placebo plus paclitaxel arm (HR=0.807, 95% CI: 0.678, 0.962; p=.0169). Grade ≥ 3 AEs occurring in >5% of patients on the ramucirumab plus paclitaxel arm were: neutropenia (40.7% ramucirumab plus paclitaxel arm; 18.8% placebo plus paclitaxel arm), leukopenia (17.4% vs 6.7%), hypertension (14.1% vs 2.4%), anemia (9.2% vs 10.3%), fatigue (7.0% vs 4.0%), abdominal pain (5.5% vs 3.3%), and asthenia (5.5% vs 3.3%). Febrile neutropenia was reported in 3.1% in the ramucirumab plus paclitaxel arm and 2.4% placebo plus paclitaxel arm.

A placebo-controlled, double-blind phase 2 study, 14T-MC-JVBT (JVBT), of ramucirumab in combination with mFOLFOX-6 as first line therapy for advanced adenocarcinoma of the esophagus, GEJ or stomach (N=168) showed no improvement in the primary endpoint of

progression-free survival. Median PFS was 6.4 months for the ramucirumab arm vs 6.7 months for the placebo arm; stratified HR=0.98, 95% CI: 0.69, 1.37; p=0.886), or the secondary OS endpoint (median OS was 11.7 months vs 11.5 months; stratified HR=1.08, 95% CI: 0.73, 1.58; p=.712), but did lead to improved PFS rate at 3 months (89.0% versus 75.3%) and an improved disease control rate (DCR)(84.5% vs 66.7%; p=0.008). The majority of patients had a primary tumor location involving the GEJ/cardia/esophagus (76.8%), with nearly half of the patients (47.6%) with a primary tumor location of esophagus. Progression-free survival was similar for all subgroups pairings with the exception of primary tumor location. In a preplanned subgroup analysis, an improvement in PFS (as assessed by HR) was observed for ramucirumab in patients with a primary tumor location of gastric/GEJ/cardia (median PFS was 8.7 months for the ramucirumab arm vs 7.1 months in the placebo arm; HR=0.77) compared to patients with a primary tumor location of esophagus (median PFS was 5.6 months vs 6.1 months; HR=1.30). A higher rate of discontinuation from study treatment for reasons other than progressive disease (PD) in the ramucirumab arm compared with the placebo arm was observed (50% vs 19%), which led to lower study drug exposure in the experimental arm. These observations may have had a negative impact on the results of the PFS assessment of the entire study population. Overall, the safety profile for ramucirumab in this study was consistent with the known safety profile of ramucirumab. The most common ≥ 3 AE (by consolidated AE) reported was neutropenia (26.8% ramucirumab arm vs 36.3% placebo arm). Fatigue (18.3% in the ramucirumab arm vs 15.0% in the placebo arm) and neuropathy (8.5% vs 11.3%) were the most common Grade ≥ 3 AEs (by consolidated term) reported at a similar frequency in each arm. The following treatment-emergent adverse events (TEAEs) (by consolidated term) were reported more frequently (≥ 5% greater) in the ramucirumab arm than in the placebo arm for thrombocytopenia (56.1% vs 38.8%), headache (23.2% vs 15.0%), hypokalemia (19.5% vs 8.8%), hypocalcaemia (9.8% vs 2.5%), and hypophosphatemia (7.3% vs 1.3%). Grade ≥ 3 adverse events of special interest (AESIs) were uncommon with the exception of hypertension (15.9% vs 3.8%).

More information about the known and expected benefits, risks, and reasonably anticipated AEs of ramucirumab are found in the Investigator's Brochure (IB). Information on AEs expected to be related to ramucirumab may be found in Section 7 (Development Core Safety Information) of the IB.

Ramucirumab has been approved by the US FDA as a single agent and in combination with paclitaxel for the treatment of patients with advanced or metastatic, gastric or GEJ adenocarcinoma after fluoropyrimidine- or platinum-containing chemotherapy (CYRAMZA package insert [PI].

The approval of ramucirumab as a single agent was based on clinical efficacy and safety demonstrated in the randomized Phase 3 study, REGARD, which compared ramucirumab monotherapy with best supportive care in patients with advanced gastric or GEJ adenocarcinoma whose disease had progressed after prior chemotherapy [7].

In both the REGARD and RAINBOW trials, which were conducted in the second-line setting, ramucirumab was administered at a dose of 8mg/kg every 2 weeks (REGARD), and 8mg/kg on Day 1 and Day 15 using a 28-day schedule (RAINBOW). In summary, the dosing regimen of

8mg/kg every 2 weeks is anticipated to produce an acceptable benefit-risk profile in patients with metastatic gastric or GEJ adenocarcinoma as second-line treatment.

2.4 Rationale for the Combination of Olaparib and Ramucirumab

The process of DNA damage repair is complex, and additional alterations beyond BRCA 1 and 2 play a role in sensitivity to PARP inhibition. This has led to the concept of "BRCAness," and we propose that the BROCA-HR panel can help identify patients with the BRCAness phenotype in addition the more typical BRCA mutations. Preclinical work has shown that hypoxia may induce BRCAness, which can potentially be taken advantage of through the combined effects of VEGF/VEGF receptor (VEGFR) and PARP inhibition.

Hypoxia has been shown to down regulate BRCA 1 expression through promoter modification by E2F4 complexes, which results in decreased homologous repair in human cancer cell lines [37-39]. Subsequent work has shown that gene silencing of BRCA 1 can occur through epigenetic modification by H3K9 methylation of the BRCA 1 promoter, which is potentiated under hypoxic conditions [38]. These modifications result in genetic instability, as cells then must rely on non-homologous DNA repair, which is more error prone. Similar findings have has also been reported for RAD51, another gene involved in the homologous repair pathway [38, 40-42].

As expected the exact opposite changes were seen in VEGF expression under hypoxic conditions, which further supports the potential synergy for PARP and VEGF/VEGFR inhibition [38]. Data also exists that PARP inhibitors themselves likely inhibit tumor angiogenesis [43]. The argument for synergy was strengthened by evidence in cancer cell lines that revealed increased lethality with PARP inhibitors in hypoxic conditions as compared to normoxic conditions [44]. Subsequently, VEGFR3 inhibition in ovarian cell lines has also been shown to result in reduced BRCA expression [45].

Based on these pre-clinical observations, a phase 2 trial comparing olaparib and cediranib to olaparib alone for metastatic ovarian cancer was recently completed. Significant improvement in progression-free survival was seen with the combination of cediranib and olaparib, and the benefit was observed for both BRCA mutated and non-BRCA mutated individuals [46]. A phase 3 study is currently ongoing to confirm these findings.

These pre-clinical and clinical observations of synergy between PARP and angiogenesis inhibition in BRCA-deficient tumors provide rationale for combining olaparib with ramucirumab in tumors characterized by defective homologous DNA repair pathway. Ramucirumab is a fully humanized IgG1 monoclonal antibody that binds to VEGFR-2 and blocks VEGF-A, VEGF-C, and VEGF-D binding and receptor-mediated pathway activation. Ramucirumab is approved for second-line therapy in gastroesophageal adenocarcinoma. In this setting ramucirumab is well tolerated and has been shown to significantly extend progression-free survival compared to best supportive care.

As noted above, the olaparib and cediranib combination resulted in high response rates regardless of the presence of BRCA mutations. Based on this we anticipate responses in both

biomarker positive and negative cohorts given the proposed synergy with this combination therapy. Thus, we propose an open-label single arm study of olaparib in combination with ramucirumab for metastatic gastric adenocarcinomas with the use of the BROCA-HR integrated biomarker, which is described in further detail below in section 2.5.1.

2.5 Correlative Studies Background

2.5.1 BROCA-HR Panel

Aim: To determine whether mutations in HRD genes confer sensitivity to ramucirumab and olaparib.

BRCA1 and *BRCA2 (BRCA1/2*) are tumor suppressor genes, in which inherited loss-of-function mutations confer a high lifetime risk of breast and ovarian carcinoma. *BRCA1/2* are key components of the BRCA-Fanconi anemia (FA) pathway, which is critical to homologous combination-mediated DNA repair. Other genes in this pathway (*BRIP1/FANCJ, PALB2/FANCN, RAD51C/FANCO, RAD51D*) also contribute to hereditary breast and ovarian cancer [47-51], and as our sequencing efforts have increased mutations in these same genes have been recognized in other cancers, including gastric cancer. The Cancer Genome Atlas Network (TCGA) suggested that up to half of serous ovarian carcinomas have homologous recombination defects (HRD), but that estimate was based on a variety of molecular findings, many with uncertain impact on DNA repair function[52]. PARP inhibitors (PARPi) demonstrate synthetic lethality in cells with HRD, including cells deficient in *BRCA1/2 [21, 53]*. Recurrent ovarian carcinomas in *BRCA1/2* mutation carriers have an approximate 40% response rate to PARPi and also have an increased response to platinum-based chemotherapy [54]. Importantly, approximately 25% of serous ovarian cancers that are wildtype for *BRCA1/2* also respond to PARPi [27].

Germline *BRCA1/2* mutations are the prototype molecular alterations that confer HRD [21, 53]. *BRCA1* and *BRCA2* somatic mutation occur in approximately 6% of ovarian cancer cases and also appear to confer sensitivity to PARPi [55]. Of note, PARPi also selectively kill cells *in vitro* that are deficient in other homologous recombination (HR) genes including *RAD51D, NBN, ATM,* and *CHEK2 [47, 56]*. Germline and somatic mutations in *BRCA1/2* and other BRCA-FA genes in ovarian carcinomas are associated with improved response to primary platinum therapy and longer overall survival [57]. Germline and somatic BRCA-FA mutations are not limited to high-grade serous ovarian carcinomas, but can be found in all histological sub-types with the exception of mucinous carcinomas [57].

In order to respond to a PARPi, cancer cells need to be deficient in HR but also proficient in the alternative error prone non-homologous end joining (NHEJ) DNA repair pathway [58, 59]. Thus, loss of HR is not, by itself, sufficient for PARPi sensitivity, and an accurate predictor of PARPi responsiveness could require assessment of many components of both the HR and NHEJ pathways. A more efficient assay, which would not require a prior knowledge of the critical elements in these DNA repair pathways, would instead measure DNA repair capacity. Recent evidence suggests that *BRCA1/2* deficient cancers exhibit global DNA alterations termed "genomic scarring" that are consistent with their reliance on the NHEJ pathway [60-62]. This genomic scar could serve as a downstream functional output to measure DNA repair capacity,

indicative of both HR deficiency and NHEJ proficiency. Therefore, mutations in NHEJ and other pathways that could affect HR as well as genomic scarring will also be evaluated as exploratory biomarkers.

Relevance

The marked susceptibility of patients with BRCA-mutated cancers has validated germline BRCA mutations as a predictive biomarker for PARPi response [63]. Other mechanisms of HRD may be a functional biomarker for response to DNA damaging agents and PARPi. Thus, it is important to identify the subset of patients have germline or somatic mutations in HRD genes and to examine their potential as predictive biomarkers. Additional exploratory biomarkers for HRD will include *BRCA1* methylation, *BRCA1* protein expression, and genomic scarring. We hypothesize that the BROCA-HR test will identify subsets of gastric cancer patients with HRD, and may yield biomarkers with potential to guide administration of this combination regimen.

Preliminary Data

BROCA-HR and genomic scarring

BROCA is a targeted capture and massively parallel sequencing assay that is capable of identifying all classes of mutations including gene rearrangements [51, 64]. Using BROCA, Walsh et al demonstrated that nearly one-fourth of women with ovarian carcinoma have germline loss of function mutations in at least 12 genes [51]. Furthermore, most of these genes are in the BRCA-FA pathway. After *BRCA1/2*, the most common genes mutated in women with ovarian cancer are *BRIP1 (FANCJ), RAD51D, RAD51C (FANCO),* and *PALB2 (FANCN) [51, 65]*. Pennington et al applied BROCA to detect somatic mutations in tumor DNA from 363 women with ovarian carcinoma. Combining germline and somatic mutations increased the fraction of cases identified with HRD to 31%, including 23% with germline and 9% with somatic mutations in FA/HR genes (and 1% with both somatic and germline mutations). The presence of either a germline or somatic FA/HR mutation is highly predictive of an improved primary response to platinum chemotherapy ($p<0.0005$) and longer overall survival ($p=.001$, Pennington, Swisher et al manuscript in progress). Germline and somatic loss of function mutations were identified in all of the 13 FA/HR genes evaluated.

Dr. Swisher's laboratory has developed a new version of BROCA (BROCA-HR) that includes many additional DNA repair genes (84 total genes), and 3000 single nucleotide polymorphisms (SNPs). Similar sequencing accuracy and sensitivity sequencing DNA is obtained from formalin fixed paraffin embedded (FFPE), fresh blood and flash frozen specimens. BROCA-HR includes genes that are targets of both somatic and germline mutations. The BROCA-HR includes genes that regulate HR or NHEJ that, if mutated, could mediate resistance to PARPi such as TP53BP1[66-68] . The BROCA design is flexible and can be altered to include any genes of research interest. The current design for BROCA-HR includes the following genes:

BROCA-HR gene list (n=84)
a. FA-BRCA HR pathway: *ATM, ATR, BABAM1, BAP1, BARD1, BLM, BRCA1, BRCA2 (FANCD1), BRIP1 (FANCJ), BRCC3, BRE, CHEK1, CHEK2, C11ORF30 (Emsy), ERCC1, ERCC4 (FANCQ), FAM175A (abraxas), FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG (XRCCC9), FANCI, FANCL, FAMCM, GEN1, MRE11A, NBN, PALB2*

(FANCO), RAD50, RAD51, RAD51C (FANCO), RAD51D, RBBP8 (CtIP), SLX4 (FANCP), UIMC1 (RAP80), XRCC2
b. DNA mismatch repair *MLH1, MSH2 (*and *EPCAM), MSH6, PMS2*
c. Other DNA repair, surveillance genes, or modifier genes : *CDK12*, *CDH4*, *HELQ, NEIL1, PPM1D, POLD1, POLE, POLQ, RIF1,TP53, ID4, PARP1, PAXIP1, POLQ, RINT1, TP53BP1, USP28, WRN, XRCC3*
d. NER genes: *ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, DDB1, XPA, XPC*
e. NHEJ genes: *DCLRE1C, LIG4, PRKDC, TOBP1, XRCC4, XRCC5, XRCC6*
f. PI3K pathway: *PTEN, PI3KCA*

2.5.2 Signature 3

Aim: To determine whether a mutational signature characteristic of HRD confers sensitivity to ramucirumab and olaparib.

Evidence of defective homologous repair has been reported in up to 12% of Gastric Tumors based on mutational signature analysis. Alexandrov et al. utilized whole genome sequencing, followed by frequency of single base substitutions to describe 21 distinct mutational signatures across 30 cancer types [69]. Cancer genomes generally carry a large number of somatic mutations, which for the most part are passenger mutations [70]. However the frequency and distribution of these single base somatic mutations creates an imprint on the cancer genome, which can provide insight into the pathogenesis of a particular tumor [71]. For example, previous work has shown that C:G > A:T substitutions occur at higher frequencies for smoking-associated lung cancers [72]. Alexandrov's work has taken this a step further by analyzing the frequencies of the 6 classes of base substitutions (C:G > A:T, C:G > G:C, C:G > T:A, T:A > A:T, T:A > C:G, T:A >G:C), which including the 5' and 3' bases yields 96 possible combinations [69]. Whole exome sequencing data from more than 7000 tumors across 30 different cancer types were analyzed, which resulted in approximately 5 million somatic substitutions as well as insertions and deletions.

After analyzing the frequency for the 96 possible combinations of base substitution it was noted that the number of somatic mutations was variable amongst the different cancer classes. This sequencing data allowed for the identification of 21 distinct mutational signatures across the 30 cancer types through the application of validated mathematical algorithms [61, 69, 71]. This same mathematical modeling allows for the quantification of each signature in a particular cancer genome as multiple signatures may contribute to a different proportion of the mutations detected in a specific tumor [70, 71]. Helleday et al. uses the analogy of a human face to help explain; the aggregate of all the somatic substitutions would represent the face, while the facial features such as the eyes, nose, and mouth would represent the extracted individual mutational signatures [71]. Some signatures were notable for a very specific base substitution, and others had a more homogenous distribution of the 96 possible combinations. While an individual signature can be seen across multiple cancers, several signatures were discovered to have strong associations to specific cancers and known driver mutations [70]. In addition to the distribution of the 96 somatic substitutions large insertions and deletions were found to have a strong association with signature 3, which was strongly associated with BRCA1 and BRCA2 mutations [12, 69].

Signature 3 was observed in BRCA-mutated ovarian, breast, and pancreatic cancers and was

characterized by a homogenous distribution of base substitutions [69]. Additionally, increased numbers of indels with overlapping microhomologies at break points were identified in signature 3 tumors [12, 69]. These findings strongly suggest that signature 3 is characteristic of a defective homologous DNA repair pathway. Subsequently, signature 3 has been described in 7-12% of gastric cancers with the majority being non-BRCA mutated, which indicates a separate defect in the homologous DNA repair pathway or additional mechanisms of BRCA silencing [12]. This offers a novel biomarker to identify tumors with defects in the homologous double-stranded DNA repair pathway that may benefit from agents targeting DNA repair pathways, specifically PARP inhibitors.

2.5.3 Immunoassay for poly-ADP-ribosylated (PAR) products:

Aim: To assess the effectiveness for olaparib and ramucirumab to inhibit DNA repair in gastric carcinoma.

Because the product of the PARP enzyme is poly-ADP-ribosylated (PAR) molecules, an immunoassay to quantify the amount of cellular PAR was developed as a clinical biomarker of PARP inhibition. Abbott Laboratories and the NCI-Frederick laboratories developed and cross-validated a quantitative immunoassay for PAR [73]. The validated assay is a sandwich enzyme chemiluminescence immunoassay employing commercially obtained antibodies to PAR, and pure PAR as a standard. Assay dynamic range is 31 to 2000 pg/ml PAR, with a lower limit of quantitation of approximately 15 pg/ml PAR. The standard curve is linear throughout the range (with an adjusted R2 typically better than 0.98). The assay uses high, midrange, and low controls produced from the human melanoma line Colo829. Specimen handling was optimized for both PBMCs and tumor needle biopsies (18 ga), and harmonized for use with the same standards and controls. Specimens could be subjected to at least 3 freeze-thaw cycles without a detectable loss of antigen binding. Assay precision was determined at both Abbott and the NCI-Frederick, to be better than 80% (estimated total imprecision at Abbott, 7% or less). Accuracy, as assessed by spike recovery of pure PAR into PBMC lysates, was 100% +/- 20%. Assay dilution linearity was established for the Colo829 controls and tumor lysates, although deviations from linearity are observed in some tumor homogenates, and assay conditions are controlled to compensate for that lack of linearity. The validated assay was used to measure PAR levels in PBMCs of healthy donors, in animal models after administration of a single and multiple dosing of ABT-888, and will be used to measure PAR in PBMCs and tumor biopsies in the proposed protocol.

2.5.4 Novel Genomic assay for "BRCAness"

Aim: To build a genomic assay for identifying BRCAness in clinical samples to identify genomically-driven mechanisms of sensitivity to PARP inhibition.

Homologous recombination pathways have been described in great detail, both in model organisms as well as in human cancer. However, despite the growing list of gene products responsible for or involved in homologous recombination-based repair, assays that reliably detect homologous recombination repair deficiency are still lacking. Therefore we will develop and perfect a sensitive DNA sequencing-based diagnostic of HR defects. Towards this goal, we will obtain whole-exome sequencing (WES) in various cancer that harbor mutations (germline or bialleleic somatic) in key DNA-repair genes.

Samples will be obtained as part of this clinical trial with the PARP inhibitor olaparib in gastroesophageal cancers. Exome wide patterns of break and repair in HR-deficiency cancers will be defined and then we will attempt to package this in a compact targeted footprint, ideally less than 100kb, so that it can be adapted to multiplexed and cell free applications in the clinic.

2.5.5 Factors demonstrating synthetic lethality with PARP inhibitors in gastric cancers.
Aim 1: Investigate the role of key signal transduction pathways in regulating the DNA damage response pathway in gastric cancer cell line models.
Aim 2: Unbiased identification of modifiers of responsiveness to PARP inhibitors.
Aim 3: Test effects of PARP inhibitors alone or in combination with other agents (based on results of Aims 1 and 2) in patient-derived xenograft models.

It has become clear that signaling through oncogenic pathways result in activation of DNA damage checkpoint response pathways. For example, acute expression of oncogenic RAS results in activation of DNA damage response (DDR) pathways, which is mediated by the ATR protein kinase and checkpoint kinases, CHK 1/2 [74, 75]. In agreement with this, inhibition of CK1 activation results in enhanced sensitivity to DNA-damaging cytotoxic agents [76]. Emerging evidence demonstrates that components of the DNA damage checkpoint response are regulated through RAS effector pathways. In particular the PI3 kinase pathway has been demonstrated to regulate ATM activity. This effect was enhanced by dual-inhibition of MEK and PI3 kinase in a melanoma model [77]. A possible role of the RAF-MEK-ERK pathway in regulating DDR is further supported by our findings demonstrating regulation of ATM protein expression by MEK as determined by Reverse-Phase Protein Analysis. In contrast to other cancers of the GI system, RAS oncogenes are rarely mutated in gastric cancers and the role and regulation of specific DDR components through oncogenic signal transduction processes in this disease is poorly understood [14]. Therefore, in Aim 1, we will investigate the role of key signal transduction pathways in regulating the DNA damage response pathway in gastric cancer cell line models. We will further seek to identify new markers of sensitivity to PARP inhibition in gastric cancer in an unbiased fashion. Previous work performed by Dr. Ashworth and colleagues identified such markers (including *NBS1, TDG, XPA,* and *MK2*) in breast cancer models using a multi-dimensional set of genomic and RNA expression data [78]. Since this correlative approach is limited in its ability to predict causality, we will focus in Aim 2 on identifying so far unknown mediators of responsiveness to PARP inhibitors in gastric cancer using a CRISPRi screening approach. In aim 3 we will test the effects of PARP inhibitors alone or in combination with other agents in PDX models. These models overcome limitation of cell line derived in vivo models (loss of characteristics of the parent tumor, lack of clinical annotation, and the limited representation of genotypes and subtypes) and closely resemble conditions in human tumors. As part of an ongoing effort, Dr. Janjigian's group at Memorial Sloan Kettering Cancer Center (MSKCC) has been able to implant 131 tumor samples from patients with esophagogastric cancers in mice were so far, with 32 resulting in established PDX tumors. Engraftment rates were 46% (orthotopic) and 26% (subcutaneous). Both normal and tumor patient DNA from patients and PDX tumor DNA are being analyzed by next generation DNA sequencing. Data so far demonstrate consistently that primary and PDX tumors exhibit similar histology, mutational profile, and copy number plots, suggesting that PDXs represent the tumors from which they are derived. To date, 10 of the 32 PDXs have been analyzed with tumors clustering with the CIN subtype, 1 with the MSI subtype and 2 were genomically stable. We are planning on obtaining fresh tumor biopsies

from selected patients with olaparib and ramucirumab to generate additional PDX models representing BRCAness genotypes.

2.5.6 T Cell receptor diversity.

Aim: To define the T cell receptor diversity of gastric cancer patients with and without BRCAness.

Humans generate T cells with a circulating diversity of > 100 x 10^6. Persistence of antigen-specific T cells is dependent on the presence of the specific antigens. If BRCAness is associated with a greater number of neoantigens, then the repertoire of T cells within these patients should reflect this increased antigenic diversity. We therefore hypothesize that patients with the BRCAness phenotype will have a higher diversity of T cell clonotypes. Moreover, if PARPi induced tumor cell lysis, this will lead to release of antigens, which could in turn be associated with treatment induced T cell repertoire diversification. To test this hypothesis, we will perform next-generation T-cell receptor sequencing on both fresh tumor samples and blood from patients with gastric cancer to assess both of these compartments. T cells see antigen through their TCR, which is comprised of two subunits, α and a β. Each is generated by a VDJ recombination event resulting in a broad range of T cell clones with different specificities. The β subunit has greater clonal diversity. We have used next-generation sequencing of the T cell receptor β chain (TCRβ) to define the diversity and frequency of T cell clones in the blood of cancer patients. The Fong lab has demonstrated that CTLA-4 blockade induces global remodeling of the T cell repertoire [79]. We found that anti-CTLA-4 administration promotes active turnover in the T cell repertoire, which increases with sequential treatments, and a net result of increased repertoire diversity overall. These changes occurred both in naïve and non-naïve T cells, the latter of which includes the antigen-experienced effector T cell population. Interestingly, maintenance of high-frequency clonotypes (greater than 1 in 1000) was associated with clinical response and improved overall survival following ipilimumab. We have since sequenced blood from patients with localized prostate cancer, metastatic castration resistant prostate cancer, or age-matched healthy men without cancer. We find that men with prostate cancer have a significantly more diverse T cell repertoire (i.e. lower clonality index). This finding would indicate that cancer can induce the diversification of the pool of circulating T cell clones in these patients. In this study, TCR diversity will be measured by the number of unique TCR, the distribution of TCR frequency, and the Shannon's diversity index [79]. We will also determine through these studies whether the circulating T cell repertoire is reflective of the T cells within the tumor microenvironment.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 The patient must have histologically confirmed, gastric carcinoma, including GEJ adenocarcinoma (patients with adenocarcinoma of the distal esophagus are eligible if the primary tumor involves the GEJ).

3.1.2 The patient has metastatic disease or locally recurrent, unresectable disease.

3.1.3 The patient must have measurable disease by RECIST v1.1. Please see Section 11 for the definition of measurable disease.

3.1.4 The patient must have experienced disease progression during or within 4 months after the last dose of chemotherapy for metastatic disease, during or within 6 months after the last dose of adjuvant chemotherapy, or have been intolerant of previous chemotherapy.

3.1.5 The patient must have experienced disease progression or intolerance as outlined above after treatment with 1 or more prior chemotherapies.

3.1.6 All previous treatments are acceptable as long as they did not contain bevacizumab, ramucirumab or PARP inhibitors.

3.1.7 Elevation in tumor markers without radiographic evidence of disease progression is not satisfactory for progression on previous treatment.

3.1.8 The patient is ≥ 18 years of age.

3.1.9 The patient has a life expectancy of ≥ 16 weeks.

3.1.10 ECOG performance status score of 0-1 (Karnofsky ≥60%).

3.1.11 Patients must have normal organ and marrow function within 28 days prior to administration of study treatment as defined below:

- Hemoglobin ≥10 g/dL with no blood transfusions (packed red blood cells and platelet transfusions) in the past 28 days.
- White blood cells (WBC) > 3 x 10^9/L
- Absolute neutrophil count (ANC) ≥ 1.5 10^9/L
- Platelet count ≥ 100 X 10^9/L
- No features suggestive of MDS/AML on peripheral blood smear or bone marrow biopsy, if clinically indicated.
- Total bilirubin ≤1.5 x the institutional upper limit of normal (ULN)
- AST (SGOT) / ALT (SGPT) ≤ 2.5 × institutional ULN unless liver metastases are present in which case they must be ≤ 5 x ULN
- Calculated serum creatinine clearance ≥ 60 mL/min/1.73 m^2
- Proteinuria with urinary protein ≤ 1+ on dipstick or routine urinalysis, or a 24-hour urine collection for protein < 1000 mg of protein in 24 hours.
- Coagulation parameters (INR, aPTT) ≤1.25 x institutional limits, except where a lupus anti-coagulant has been confirmed or the patient is on warfarin. Patients on

full dose anticoaugulation must be on a stable dose for at least 14 days. If receiving warfarin, the patient must have an INR ≤ 3.0 without any evidence of active bleeding within 14 days prior to first dose of study treatment or a pathologic condition that carries a high risk of bleeding (tumor involvement with major blood vessels or varicies).

3.1.12 Postmenopausal or evidence of non-childbearing status for women of childbearing potential a negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day 1. Postmenopausal is defined as:

Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments.

Luteinizing hormone (LH)and Follicle stimulating hormone (FSH) levels in the post menopausal range for women under 50.

Radiation-induced oophorectomy with last menses > 1 year ago.

Chemotherapy-induced menopause with > 1 year interval since last menses.

Surgical sterilization (bilateral oophorectomy or hysterectomy).

3.1.13 The effects of olaparib and ramucirumab on the developing fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception including hormonal, barrier, or abstinence. Contraception must be started prior to study enrollment. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Both men and women treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of the study participation, and for 3 months after completion of olaparib and ramucirumab administration. Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of **two highly effective forms of contraception in combination**, throughout the period of taking study treatment and for 3 months after last dose of study drug(s) to prevent pregnancy in a partner.

3.1.14 Ability to understand and the willingness to sign a written informed consent document.

3.1.15 The patient must be willing to undergo a biopsy prior to treatment, an on treatment biopsy at week 16 is optional if felt to be safe in the opinion of the investigator.

3.1.16 For inclusion into optional exploratory genetic and biomarker research, patients must fulfill the following criteria:

- Provision of informed consent for genetic research
- Provision of informed consent for biomarker research

If a patient declines to participate in the optional exploratory genetic research or the optional biomarker research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other parts of the study.

3.1.17 Patients must be able to tolerate oral medications by mouth, and not have a gastrointestinal illness that would preclude absorption of olaparib.

3.1.18 Adequately controlled blood pressure (BP) <140 mmHg (systolic) and <90 mmHg (diastolic) taken in the clinic setting by a medical professional within 2 weeks prior to starting study. Patients with hypertension may be managed with up to a maximum of 3 antihypertensive medications. A cardiologist or blood pressure specialist must evaluate patients who are on 3 antihypertensive medications within 4 weeks of enrollment.

3.1.19 Patients who have the following risk factors are considered to be at increased risk for cardiac toxicity and must have documented LVEF by Echocardiogram greater than institution's lower limit of normal (or 55% if threshold for normal not otherwise specified by institutional guidelines) obtained within 3 months.

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- A New York Heart Association (NYHA) classification of II controlled with treatment (See Appendix B)
- Prior central thoracic radiation therapy (RT), including RT to the heart.
- History of myocardial infarction within 12 months (patients with history of myocardial infarction within 6 months are excluded)

3.2 Exclusion Criteria

3.2.1 Patients with untreated brain metastases are excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression are also excluded unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

3.2.2 Patients who have not recovered from adverse events due to prior anti-cancer therapy (i.e., have residual toxicities > CTCAE Grade 1 or baseline, with the exception of alopecia).

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

3.2.4 The patient has experienced any grade 3-4 gastrointestinal bleeding within 3 months prior to randomization.

3.2.5 The patient has experienced any arterial thrombotic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to enrollment.

3.2.6 The patient has an ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or hemorrhagic disorder, or any other serious uncontrolled medical disorder in the opinion of the investigator.

3.2.7 The patient has an ongoing or active psychiatric illness or social situation that would limited compliance with study requirements.

3.2.8 Clinically significant peripheral vascular disease or vascular disease (abdominal aortic aneurysm >5cm) or aortic dissection). If known history of abdominal aortic aneurysm with ≥ 4cm in diameter, all of the following must be met.

- An ultrasound within the last 6 months required to document that it is ≤5cm
- Patient must be asymptomatic from the aneurysm
- Blood pressure must be well controlled as defined in this protocol (see section 6).

3.2.9 The patient has uncontrolled or poorly controlled hypertension despite standard medical management as defined in this protocol (see section 6).

3.2.10 NYHA classification of III or IV.

3.2.11 A resting EKG with a QTC ≥ 470 msec detected on 2 or more time points within a 2 hour period or family history of long QT syndrome. If the EKG demonstrates QTC ≥ 470 msec, the patient will only be eligible if a repeat EKG demonstrates QTC ≤ 470 msec.

3.2.12 History of hypertensive crisis or hypertensive encephalopathy within 3 years.

3.2.13 Major surgery within 28 days of starting study treatment and patients must have recovered from any effects of any major surgery.

3.2.14 An open biopsy, non-healing wound, ulcer or significant traumatic injury within 28 days prior to starting treatment (percutaneous, endobronchial, and endoscopic biopsies are allowed).

3.2.15 The patient has received chemotherapy, radiotherapy (except for palliative reasons), immunotherapy, or targeted therapy for gastric cancer within 3 weeks of study treatment.

3.2.16 The patient has received any investigational therapy within 4 weeks of enrollment.

3.2.17 The patient has received prior therapy with bevacizumab, ramucirumab or any PARP inhibitor, including olaparib.

3.2.18 Patients must not have evidence of coagulopathy or bleeding diathesis. Therapeutic anticoagulation for prior thromboembolic events is permitted. The clinical indication for therapeutic anticoagulation must be clearly documented prior to enrollment and must be discussed with the PI. Due to risk of serious bleeding with ramucirumab, patients on greater than or equal to 2 anti-thrombotic agents, including but not limited to anti-platelet agents (NSAIDS/aspirin, clopidogrel), heparin, low molecular weight heparin, warfarin and a direct thrombin inhibitor will be excluded.

3.2.19 The patient has elective or planned major surgery to be performed during the course of the clinical trial.

3.2.20 History of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib and ramucirumab.

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

3.2.22 Patients with a known hypersensitivity to the combination/comparator agent.

3.2.23 Pregnant or breast feeding women are excluded from this study because olaparib and ramucirumab have the potential for teratogenic or abortifacient effects.

3.2.24 Immunocompromised patients, this includes HIV-positive patients, because of the potential for interaction with antiretroviral therapy and ramucirumab and/or olaparib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.25 Patients with a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as detectable HCV RNA) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

3.2.26 The patient has known and active alcohol or drug dependency.

3.2.27 The patient has a concurrent active malignancy other than treated non-melanoma skin cancers or in situ neoplasm. A patient with a prior history of malignancy is eligible, provided that they have been free of disease for ≥ 5 years.

3.2.28 Patients may not have features suggestive of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) on peripheral blood smear or bone marrow biopsy, if clinically indicated.

3.2.29 Patients may not have had a prior allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).

3.2.30 Patients may not have current signs and/or symptoms of bowel obstruction within 1 month prior to starting study drugs, except if it was a temporary incident (improved within <24 hr with medical management).

3.2.31 History of hemoptysis within the last 1 month.

3.2.32 History of abdominal fistula, intra-abdominal abscess, or gastrointestinal perforation within the last 3 months.

3.2.33 Dependency on IV hydration > 1 day per week within the screening period.

3.2.34 Participants receiving any medications or substances that are strong inhibitors or inducers of CYP3A4/5 are ineligible. The required washout period prior to starting treatment is 2 weeks for CYP3A inhibitors, 3 weeks for CYP3A inducers, and 5 weeks for enzalutamide. Dihydropyridine calcium-channel blockers are permitted for management of hypertension.

3.2.35 Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing please refer to inclusion criteria 3.1.12).
3.2.36 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
3.2.37 Previous enrollment in the present study.
3.2.38 Current use of natural herb products or other complementary alternative medications. If used previously, patients must have at least 1-week washout and must stop using them while participating in this study.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	

Documentation Required	IVR	NPIVR	AP	A
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov mailto:>.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 10066 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-CT 018, and protocol #10066.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 10066 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory

Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex websitehttp://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 10 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Dose Escalation Schedule			
Dose Level	**Dose***		
	Olaparib (mg)	**Ramucirumab *(mg/kg)***	***N/A***
-2	100 mg twice daily, orally (tablet)	8 mg/kg every 2 weeks, intravenous	
-1	150 mg twice daily, orally (tablet)	8 mg/kg every 2 weeks, intravenous	
1 (starting dose)	200 mg twice daily, orally (tablet)	8 mg/kg every 2 weeks, intravenous	
2	300 mg twice daily, orally (tablet)	8 mg/kg every 2 weeks, intravenous	

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Olaparib	Swallow whole, do not chew or crush. Take AM and PM dose 12 hours apart, doses can be taken with or without food. The patient will be requested to maintain a medication diary of each dose medication. This medication diary will be returned to clinic staff at the end of each course (Appendix C).	Up to 300mg (tablet formulation)	Oral	*Twice daily*	*14 days (2 weeks)*
Ramucirumab	Intravenous antihistamine (H1 receptor antagonist); for grade 1-2 infusion reactions dexamethasone and acetaminophen are added.	8mg/kg	Through intravenous line	*Day 1 every 2 weeks*	

5.1.1 *CTEP IND Agent(s)*

5.1.2 Olaparib

For the phase 1 dose escalation, olaparib dosing will be increased in a 3+3 dose escalation with doses of 200mg and 300mg twice daily (See 6.0). In phase 2, after biopsy for the BROCA-HR panel patients will receive olaparib dose TBD within 14 days of biopsy. The olaparib will be given at the appropriate dose level orally continuously twice daily, with doses taken at the same times each day 12 hours apart. The olaparib tablets can be taken with or without food and should be swallowed whole with water and never chewed, crushed, dissolved or divided. The olaparib will be dispensed at the start of each cycle. Patients will be provided with a pill diary. Patients will be advised to avoid grapefruit juice while on study due to P450 interactions.

If difficulty tolerating oral medications and vomiting occurs the vomited dose should not be made up. Should an enrolled patient miss a scheduled dose the patient will be allowed to take the dose up to a maximum of 2 hours after that normally scheduled dose time, but if greater than 2 hours the patient should wait until their next allotted dose time.

Dose Reductions
For guidance on dose reductions for management of AEs refer to section 6.

Renal Impairment
If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥ 60 ml/min/1.73 m^2), retesting should be performed promptly. In the instances where the CrCl falls to between 31 and 50 ml/min/1.73 m^2 the olaparib dose will be reduced by one dose level (see section 6).

5.1.3 Ramucirumab

For both the phase 1 dose escalation and the phase 2, ramucirumab will be dosed at 8 mg/kg on day 1 of each 2-week cycle. Ramucirumab at the appropriate dose level will be delivered intravenously over 60 minutes (+/- 15 minutes) through either a peripheral IV or central line. (Please refer to the ramucirumab package insert).

5.1.4 Premedication for Ramucirumab

Premedication is required for all patients prior to each infusion of ramucirumab. The recommended agents are histamine (H1) antagonists, such as diphenhydramine chloride. Additional premedication may be given at the investigator's discretion (please refer to ramucirumab package insert). All premedication administered must be documented in the case report forms.

5.1.5 Other Modality or Procedures

N/A

5.2 Dose Escalation

A 3+3 dose escalation scheme will be used for olaparib in phase 1 with a plan to only escalate by one dose level. A definition of adverse events is included at the bottom of this section. Management and dose modifications associated with adverse events are outlined further in Section 6. With a 3+3 dose escalation design if no dose-limiting toxicity (DLT) is observed a total of 9 patients would be enrolled. However, if DLTs are observed during dose escalation 9-12 patients could be enrolled depending on whether DLTs were seen at one or both dose levels. If 2 or more DLTs are observed in the first cohort the study would de-escalate the dose. There are 2 dose levels below the starting dose (dose level -1 and dose level -2), and this could take a maximum of 18 patients if DLTs were seen at all dose levels. A schema for the 3+3 design is provided below, and the starting dose of olaparib is 200 mg twice daily as outlined in Section 6. The maximum dose of olaparib tested in this study will be an increase of one dose level to olaparib 300 mg twice daily, which is the maximum tolerated dose per the olaparib IB. Even if no DLTs are observed, the dose of olaparib will not be increased beyond 300 mg twice daily (dose level 2) in this study.

The DLT evaluation period is 28 days and dose escalation will proceed according to the following scheme and DLT definitions are defined below. A patient is evaluable for DLT if he/she receives 2 doses (100%) of ramucirumab and 45 doses (80%) of olaparib within the first 28 days OR he/she experiences a DLT. If this minimum amount of treatment is not reached due to treatment related AEs, this is considered a DLT. However, patients who fail to achieve this minimum amount of treatment due to reasons that are clearly unrelated to treatment (e.g. error on part of patient or outside physician) would be replaced.

Due to the non-overlapping toxicity profiles of olaparib and ramucirumab the likelihood for DLT is estimated at 15 to 25%. The doses of olaparib and ramucirumab will not be increased beyond the previously established maximally tolerated doses as described in the respective investigator brochures. In the REGARD study, which evaluated ramucirumab monotherapy in gastric cancer, it was well tolerated with no increase in $\geq$ grade 3 AEs as compared to placebo. Similarly in Study 19, which evaluated olaparib monotherapy in ovarian cancer it was well tolerated with $\geq$ grade 3 AEs 15% higher than the placebo group.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level. The dose of olaparib will not be increased beyond dose level 2. If 0 out of 3 DLTs are observed at dose level 2 an additional 3 patients will be enrolled at this dose level.
≥2	Dose escalation will be stopped. This dose level will be

	declared the maximally administered dose[1] (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if 3 or fewer patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose[1]. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at dose level 2 or at the highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose[2]. At least 6 patients must be entered at the recommended phase 2 dose. The olaparib dose will not be escalated beyond dose level 2. If 0 out of 3 DLTs are observed at dose level 2, an additional 3 patients will be enrolled.
[1] Maximum administered dose: The highest dose level of olaparib that 2 or more patients suffers a DLT (or 300 mg twice daily of olaparib if no DLTs are observed). [2] Recommended phase 2 dose: The highest dose level of olaparib that ≤1 out of 6 patients suffers a DLT.	

Definition of Dose Limiting Toxicities

Non-Hematologic:
Any grade 3-4 non-hematologic toxicity at least "possibly related" to the combination of olaparib and ramucirumab occurring from cycle 1 day 1 through cycle 2 day 2 during phase 1 will be considered a DLT with the following exceptions:

1. Grade 3 toxicity that lasts ≤ 2 days for nausea, vomiting, fatigue, diarrhea, constipation or anorexia will not be considered a DLT.
2. Grade 3 hypertension will not be considered a DLT unless it persists for ≥ 14 days despite optimal medical management.
3. Transient (≤ 7 days) Grade ≥ 3 elevations in AST and/or ALT without other evidence of hepatic injury will not be considered a DLT.
4. A subject did not receive at least 45 doses (80%) of olaparib or 2 doses (100%) of ramucirumab up to and including cycle 2 day 1 (i.e., other AEs not attributed as DLTs and/or dosing lab eligibility not met) will be considered a DLT.

Hematologic:
Any grade 4 hematologic toxicity (except lymphopenia) that lasts ≥ 7 days at least "possibly related" to the combination of olaparib and ramucirumab occurring from cycle 1 day 1 through cycle 2 day 2 during phase 1 will be considered a DLT with the following exceptions:

1. Thrombocytopenia grade ≥ 3 with clinically significant bleeding will be considered a

DLT.
2. Febrile neutropenia (a single temperature of 38.3°C (101°F) or more orally) or 38.0°C (100.4°F) or more over one hour and ANC < 1.0 x 10^9 / L will be considered a DLT.
3. Grade 3 neutropenia that lasts ≥ 14 days will be considered a DLT.

5.3 Dose Expansion:

After completion of the phase 1 portion of the study the maximum safe dose of olaparib will be used for phase 2. An additional 40 patients will be enrolled for phase 2 for treatment with combined olaparib (dose TBD) and ramucirumab 8 mg/kg. During phase 2 patients will continue to be monitored for occurrence of DLT. If ≥ 2 of the first 6 patients or ≥ 2 of patients 7-12 experience a DLT, the Principal Investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the recommended phase 2 dose. Monitoring of all safety and toxicity data is done by the Principal Investigator and the corresponding organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. The adverse event CRF is used for routine AE reporting in Rave. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

5.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of olaparib and ramucirumab with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. In vitro studies demonstrate that olaparib is primarily metabolized by CYP 3A4/5 enzymes. Potent inhibitors or inducers of CYP 3A4/5 are prohibited. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix D (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

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

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

Administration of other anti-cancer agents
Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or

denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

Subsequent therapies for cancer
Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the exploratory assessments of OS.

Medications that may NOT be administered
No other chemotherapy, immunotherapy, hormonal therapy or other novel agent is to be permitted while the patient is receiving study medication.

5.5 Safety Monitoring

- Laboratory safety assessment: Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each treatment visit and when clinically indicated. If absolute differentials are not available, please provide % differentials. Coagulation [activated partial thromboplastin time {APTT} and international normalized ratio {INR}] will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patient taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

- Biochemistry assessment for safety (sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin and lactic dehydrogenase [LDH]). All should be performed at each treatment visit.

- Urinalysis by dipstick should be performed at baseline. A urine dipstick for protein should be performed for on treatment visits or full urinalysis may be obtained if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

- Bone marrow or blood cytogenetic samples should be collected for patients with prolonged hematologic toxicities.

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated. Any clinical significant abnormal laboratory values should

be repeated as clinically indicated.

- In case a subject shows an AST or ALT please refer to section 6 for management considerations.

- Resting 12-lead EKG:

EKGs are required within 7 days prior to starting study treatment and when clinically indicated.

Twelve-lead EKGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The investigator or designated physician will review the paper copies of each of the timed 12-lead EKGs on each of the study days when they are collected.

EKGs will be recorded at 25 mm/sec. All EKGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE. The original EKGs must be stored in the patient medical record as source data.

- Serum or urine pregnancy test:

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

- Bone marrow or blood cytogenetic analysis:

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

- Thyroid Function:

Thyroid function should be monitored per the ramucirumab (CYRAMZA) package insert.

5.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Concurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent
- Severe non-compliance with the study protocol.
- Bone marrow findings consistent with myelodysplastic syndrome (MDS) / acute myeloid leukemia (AML).

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.7 Duration of Follow Up

- Patients who are off study treatment due to disease progression will be seen at 4 weeks for a post treatment visit, and will continue to be followed for survival.
- Patients who discontinue the study treatment for reasons other than disease progression will be seen at 4 weeks after discontinuing study treatment and continue to undergo radiographic tumor assessment until radiographic documentation of disease progression every 6 weeks, or earlier if clinically indicated, or until overall study completion, whichever comes first.

- Patients who discontinue the study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event or until radiographic documentation of disease progression as noted above.
- Patients who are discontinued from study drugs will be followed for survival every 3 months.

6. DOSING DELAYS/DOSE MODIFICATIONS

The dose levels and general approach to dose modification of olaparib and ramucirumab combination is described in the tables below. Ramucirumab will be maintained at standard dose of 8 mg/kg, and olaparib will be decreased in the event of AEs. The recommended phase 2 dose for olaparib is TBD based on phase 1 of the study.

6.1 Olaparib and Ramucirumab Dose Modification Tables

Olaparib Dosing for Phase 1 and Phase 2:

Dose Level	Olaparib Dose	Dose Reduction 1	Dose Reduction 2
-2	100 mg, twice daily	Off study treatment	--
-1	150 mg, twice daily	100 mg, twice daily	Off study treatment
1	200 mg, twice daily	150 mg, twice daily	100 mg, twice daily
2	300 mg, twice daily	200 mg, twice daily	150 mg, twice daily

Ramucirumab Dosing for Phase 1 and Phase 2:

Dose Level	Ramucirumab Dose
1 (starting dose for both phase 1 and phase 2)	8 mg/kg, every 2 weeks

General Management of Adverse Events:

Patients experiencing ongoing clinical benefit who experience a related AE where continuation of one of the drugs is considered, in the judgment of the treating investigator AND study PI, to be potentially life-threatening or with the potential for long-term harm to the patient, may be allowed to continue on the unrelated drug after discussion with the study PI.

6.2 General Management of Adverse Events for Phase 1 and 2

The DLT definitions are provided in section 5.2 and the DLT period for phase 1 is specified to be 28 days. Patients that miss > 11 doses of olaparib in the 28 day DLT period for drug related AEs despite appropriate supportive care and causality investigation will be permanently discontinued from olaparib and ramucirumab therapy.

Patients experiencing ongoing clinical benefit who experience a related AE that would necessitate stopping study treatment may be allowed to continue on the unrelated drug if felt to be in the best interest of the patient by the treating investigator after discussion with the study PI

General Management of Non Hematologic Adverse Events (see below for specific AE management tables for select toxicities).

Observation	Action
Grade 1 AE resolves promptly with supportive care	No change in dose
Any grade 2 non-hematologic AE related to olaparib or ramucirumab that resolves within 5 days with appropriate supportive care (excluding hypertension or other AEs with specific management instructions outlined below, or easily correctable asymptomatic grade 2 abnormalities).	Hold study drugs[1] until toxicity resolves to ≤ grade 1. Treatment may be restarted at the same dose without dose reduction.
Any grade 2 non-hematologic AE related to olaparib or ramucirumab that persists more than 5 days despite appropriate supportive care (excluding hypertension or other AEs with specific management instructions outlined below, or easily correctable asymptomatic grade 2 abnormalities).	Hold study drugs[1] for up to 14 days until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower for olaparib as per dose reduction levels above[2]. The overall PI of the study should be informed regarding all dose modifications. Patients whose toxicity has not resolved after 14 days will be permanently discontinued from olaparib and ramucirumab therapy. Patients experiencing persistent grade 2 fatigue that is felt to be acceptable by both patient and treating investigator may continue on study drug without dose hold or reduction at the treating investigator's discretion.
Any ≥ grade 3 non-hematologic AE (excluding grade 3 hypertension or easily correctable grade 3 abnormalities for ≤ 2 days as outlined in section 5.2). Refer to section 5.2 for DLT criteria.	Hold study drugs[1] for up to 14 days until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower for olaparib, as per the dose reduction levels above[2]. The overall PI of the study should be informed regarding all dose modifications.
• Grade 3 or 4 non-hematologic AE related to olaparib or ramucirumab lasting >14 days despite maximum supportive care and treatment being held[3]. Refer to section 5.2 for DLT lcriteria. • Grade 3 or 4 non-hematologic AE related to olaparib and ramucirumab that occurs at the lowest reduced dose level.	The patient will be permanently discontinued from olaparib and ramucirumab therapy[4].
[1]At the discretion of the investigator, the study drugs may be held or dose modified	

independently if the observed toxicity is attributed to only one of the drugs, while the patient continues to receive the drug not associated with the observed toxicity. The time a given drug is held should not exceed 14 days.
[2]Patients who are at the lowest dose reduced level may have their drug resumed at that dose level after discussion with overall PI.
[3]Excluding hypertension. For thromboembolic events, treatment may be resumed at the discretion of the investigator once patient is asymptomatic.
[4]At the discretion of the investigator the patient may continue to receive the drug not associated with the observed toxicity as monotherapy after a discussion with the overall PI.

6.3 Management of Specific Adverse Events for Phase 1 and 2:

Please refer to section 5.2 for a definition of DLTs in the 28 day DLT period for phase 1.

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

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

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered.

Nausea	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
≤ Grade 1	No change in dose.	No change in dose
Grade 2	If it lasts ≤ 5 days, hold until ≤ grade 1 and resume at same dose level. If it lasts ≥ 6 days hold* up to 14 days until ≤ grade 1 and treatment may be restarted at one dose level lower.	No change in dose**
Grade 3	Hold* until ≤ Grade 1. Resume at one dose level lower.	No change in dose**
Grade 4	N/A	N/A
*Patients requiring a delay of >2 weeks should be permanently discontinued from olaparib. **At the discretion of the investigator the patient may continue to receive ramucirumab if it is not associated with the observed toxicity.		

Nausea	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
Recommended management: Daily serotonin (5-HT3) antagonists are recommended for nausea management with break through treatment options including prochlorperazine, benzodiazepines, steroids, cannabinoids, and atypical antipsychotics.		

Vomiting	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucriumab**
≤ Grade 1	No change in dose	No change in dose
Grade 2	If it lasts ≤ 5 days, hold until ≤ grade 1 and resume at same dose level. If it lasts ≥ 6 days hold* up to 14 days until ≤ grade 1 and treatment may be restarted at one dose level lower.	No change in dose**
Grade 3	Hold* until ≤ grade 1. Resume at one dose level lower.	No change in dose**
Grade 4	Hold* until ≤ grade 1. Resume at one dose level lower.	No change in dose**
*Patients requiring a delay of >2 weeks should be permanently discontinued from olaparib. **At the discretion of the investigator the patient may continue to receive ramucirumab if it is not associated with the observed toxicity.		
Recommended management: antiemetics.		

Diarrhea	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
≤ Grade 1	No change in dose.	No change in dose
Grade 2	If it lasts ≤ 5 days, hold until ≤ grade 1 and resume at same dose level. If it lasts ≥ 6 days hold* up to 14 days until ≤ grade 1 and treatment may be restarted at one dose level lower.	No change in dose**
Grade 3	Hold* until ≤ grade 1. Resume at one dose level lower.	No change in dose**
Grade 4	Hold* until ≤ grade 1. Resume at one dose level lower.	No change in dose**
*Patients requiring a delay of >2 weeks should be permanently discontinued from olaparib. **At the discretion of the investigator the patient may continue to receive ramucirumab if it is not associated with the observed toxicity.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours)		

Diarrhea	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
Adjunct anti-diarrheal therapy is permitted and should be recorded when used. Appendix E includes instructions for diarrhea management for the patient, and should be provided to the patient.		

Leukopenia	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose**
Grade 3	Hold* until ≤ grade 2. Resume at one dose level lower.	No change in dose**
Grade 4	Hold* until ≤ grade 2. Resume at one dose level lower.	No change in dose**
*Patients requiring a delay of >2 weeks despite appropriate supportive care and causality investigation should permanently discontinue olaparib. Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Olaparib should be discontinued permanently if blood counts do not recover to CTC grade 1 or better within 4 weeks of dose interruption. **At the discretion of the investigator the patient may continue to receive ramucirumab if it is not associated with the observed toxicity.		
Insert any recommended management guidelines, if appropriate.		

Neutropenia (	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose**
Grade 3	Hold* until ≤ grade 2. Resume at one dose level lower.	No change in dose**
Grade 4	Hold* until ≤ grade 2. Resume at one dose level lower.	No change in dose**
*Patients requiring a delay of >2 weeks despite appropriate supportive care and causality investigation should be discontinued from olaparib. Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Olaparib should be discontinued permanently if blood counts do not recover to CTC grade 1 or better within 4 weeks of dose interruption. **At the discretion of the investigator the patient may continue to receive ramucirumab if it is		

Neutropenia (	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
not associated with the observed toxicity.		
Insert any recommended management guidelines, if appropriate.		

Febrile Neutropenia	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
≤ Grade 1	N/A	N/A
Grade 2	N/A	N/A
Grade 3	Off protocol therapy.	No change in dose**
Grade 4	Off protocol therapy.	No change in dose**
*Patients requiring a delay of >2 weeks should be permanently discontinued from olaparib. **At the discretion of the investigator the patient may continue to receive ramucirumab if it is not associated with the observed toxicity.		
Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.		

Anemia	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
Hemoglobin ≥ 10	No change in dose	No change in dose
Hemoglobin < 10 but ≥ 8 g/dl (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgment to continue olaparib with supportive treatment (e.g. transfusion) or interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if hemoglobin has recovered to > 9 g/dl. **Subsequent occurrences:*** If hemoglobin < 10 but ≥ 9 g/dl investigator judgment to continue olaparib with supportive treatment (e.g. transfusion) or dose interrupt (for a maximum of 4 weeks) and upon recovery dose reduction may be considered by 1 dose level as a	No change in dose**

Anemia	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
	first step and 2 dose levels as a second step. If Hemoglobin < 9 but ≥ 8 g/dl dose interrupt (for max of 4 weeks) and continue with supportive treatment (e.g. transfusion) until hemoglobin ≥ 9 and upon recovery dose reduction may be considered by 1 dose level as a first step and 2 dose levels as a second step.	
Hemoglobin < 8 g/dl (CTCAE Grade 3)*	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to hemoglobin ≥ 9 g/dl. Upon recovery dose reduce by one dose level as a first step and 2 dose levels as a second step.	No change in dose**
*Patients requiring a delay of > 4 weeks and/or red blood cell transfusion dependence despite appropriate supportive care and causality investigation should be permanently discontinued from olaparib. Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. **At the discretion of the investigator the patient may continue to receive ramucirumab if it is not associated with the observed toxicity.		
Packed red blood cell transfusions, if indicated, should be done according to local hospital guidelines.		

Thrombocytopenia	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	No change in dose**
Grade 3	Hold* until ≤ grade 1. Resume at one dose level lower.	No change in dose**
Grade 4	Hold* until ≤ grade 1. Resume at one dose level lower.	No change in dose**
*Patients requiring a delay of >2 weeks and/or platelet transfusion dependence despite		

Thrombocytopenia	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
appropriate supportive care and causality investigation should be permanently discontinued from olaparib. Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Olaparib should be discontinued permanently if blood counts do not recover to CTC gr 1 or better within 4 weeks of dose interruption. **At the discretion of the investigator the patient may continue to receive ramucirumab if it is not associated with the observed toxicity.		
Platelet transfusions, if indicated, should be done according to local hospital guidelines.		

Hypertension:

Only modifications in ramucirumab will be modified for hypertension, and olaparib doses will not be reduced unless other toxicities are experienced.

Hypertension	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	No change in dose**	No change in dose, but if persists ≥ 14 days after initiation of optimal medical management, hold* until ≤ grade 1. If ramucirumab discontinued the treating physician and study PI will discuss continuing olaparib monotherapy.
Grade 4	No change in dose**	Discontinue ramucirumab and discussion between treating physician and PI continuing on olaparib monotherapy.
*Patients requiring a delay of >4 weeks should discontinue ramucirumab. **At the discretion of the investigator the patient may continue to receive olaparib if it is not associated with the observed toxicity after discussion with the overall study PI.		
If hypertension grade 2: Initiate blood pressure (BP) medication for first-line treatment. Escalate dose of medication in stepwise fashion until BP is controlled or at a maximum dose. If BP is not controlled to <140/90 mmHg with one drug regimen, then add a second agent. If hypertension grade 3: Maximize 2 drug regimen. Suggestions: ACE inhibitor plus beta blocker. Escalate doses of existing medication until BP is controlled or at a maximum dose. If BP is not controlled to <140/90 with two drug regimen then add a third agent. Additional BP meds up to 4 may be maximized to control BP. If hypertension grade 4: Initiate treatment as inpatient hospital admission for ICU management, IV therapy as necessary.		

Proteinuria	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
1+ Proteinuria	No change in dose	No change in dose
≥ 2+ Proteinuria	No change in dose	Continue as scheduled, and conduct a 24-hour urine collection prior to subsequent treatment. If <2 g/24 hours continue without dose interruption, if 2-3 g/24 hours hold until proteinuria ≤ 1+ or < 2 g/24 hours.. Resume at same dose level.**
Grade 4	N/A	N/A
*Patients requiring a delay of >2 weeks should discontinue ramucirumab. **For patients with 2+ proteinuria on urine dipstick a 24 hour urine collection will be conducted. If the protein level is < 2 g/24 hours the patient will continue on the same dose without interruption. If the protein level is 2-3 g/24 hours, ramucirumab will be held for up to 2 weeks and a 24 hour urine protein will be repeated. The patient will be discontinued permanently from ramucirumab if the 24 hour urine protein level is > 3 g/24 hours.		
If proteinuria grade ≥ 2: consider consultation with nephrologist.		

Decrease in LVEF:
Patients who have any of the following should undergo an echocardiogram (ECHO) at baseline and every 4 cycles while on study:

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- NYHA classification of II controlled with treatment (see Appendix B)
- Prior central thoracic radiation
- History of myocardial infarction within the prior 12 months
- Prior history of impaired cardiac function

The decision to continue to hold olaparib/ramucirumab is based on the LVEF compared to the institutional lower limit of normal and change in ejection fraction from screening, according to the following table. If the institution's lower limit of normal is not specified, an LVEF of 55% should be considered the threshold.

Decreased Left Ventricular Ejection Fraction	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
<10% from screening*	No change in dose.	No change in dose.
10-19% from screening*	No change in dose.	No change in dose and repeat echocardiogram after 2 additional cycles.

Decreased Left Ventricular Ejection Fraction	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
≥ 20% from screening*	No change in dose.	Hold treatment and repeat echocardiogram in 10-14 days. If decrease in EF remains ≥ 20% from screening, discontinue ramucirumab and discussion between treating physician and PI about continuing olaparib monotherapy.**
*If no screening ECHO the change should be calculated from prior patient ECHO or if not available, the institutional lower limit of normal. **Repeating ECHO will be at discretion of the treating physician.		
If baseline cardiac dysfunction or decreased ejection fraction: Hold treatment as outlined and consider consultation with a cardiologist.		

Decrease in Creatinine Clearance

Creatinine Clearance	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
CrCl ≤ 30	Hold* until CrCl > 30	Hold* until CrCl > 30
CrCl 31-50	Decrease by one dose level	Continue at same dose level
CrCl 51-59	No change in dose.	No change in dose.
CrCl ≥ 60	No change in dose.	No change in dose.
*Patients requiring a delay of >2 weeks should be discontinued from both olaparib and ramucirumab.		

Infusion Reaction

Infusion Reaction	**Management/Next Dose for Olaparib**	**Management/Next Dose for Ramucirumab**
Grade 1-2	No change in dose	Reduce the infusion rate of ramucirumab by 50%.
Grade 3-4	No change in dose.	Permanently discontinue ramucirumab.
*Patients requiring a delay of >2 weeks should be discontinued from ramucirumab.		

Gastrointestinal Perforation.

Gastrointestinal perforations have been observed in patients receiving ramucirumab, most commonly related to the primary tumor. Ramucirumab should be permanently discontinued in those patients who experience a gastrointestinal perforation or fistula.

Hemorrhage and arterial thromboembolic events (ATEs)
Hemorrhage and arterial thromboembolic events have been observed with ramucirumab. Ramucirumab will be permanently discontinued in patients who experience these types of events.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.
Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician."

Olaparib adverse events of special interest

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

ANY event of MDS/AML, new primary malignancy, or pneumonitis should be report to CTEP whether it is concered a non-serious AE [eg non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm.

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

There are currently no identified OAEs for olaparib.

Overdose of olaparib

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

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately. An overdose with associated AEs should be recorded.

Interruptions for intercurrent non-toxicity related events

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

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

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

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

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) in addition to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. If this CAEPR is part of a

combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 CAEPR for Olaparib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Olaparib (AZD2281, NSC 747856)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aequidelines.pdf for further clarification. *Frequency is provided based on 3449 patients.* Below is the CAEPR for Olaparib (AZD2281).

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, July 1, 2021[1]

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
Abdominal pain			***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Upper respiratory infection		
	Urinary tract infection		
INVESTIGATIONS			
	Creatinine increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
		Platelet count decreased	
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	

NOTE: New Primary Malignancies other than MDS/AML
New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented *BRCA* mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib.

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on olaparib (AZD2281) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that olaparib (AZD2281) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Enterocolitis; Esophageal stenosis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Obstruction gastric; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fever; Malaise; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Dermatitis radiation; Fracture; Gastrointestinal anastomotic leak; Injury, poisoning and procedural complications - Other (vena cava injury); Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Hemoglobin increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Bone pain; Generalized muscle weakness; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain; Rotator cuff injury; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (decreased glomerular filtration rate); Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Pruritus
VASCULAR DISORDERS - Arterial thromboembolism; Flushing; Hot flashes; Hypertension; Hypotension; Peripheral ischemia; Thromboembolic event

Note: Olaparib (AZD2281) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 Please see the October 2016 FDA-approved package insert for ramucirumab for a list of the associated AEs.

7.2 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. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined below.

- **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.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the

following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI 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.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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 to the NCI via electronic submission 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	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically 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.

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

Expedited 24-hour notification followed by complete report within 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

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

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> 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 using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 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.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

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

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

7.6 Second Malignancy

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

8. 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.

8.1 CTEP IND Agent(s)

8.1.1 CTEP IND Olaparib (NSC 747856)

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

Other Names: AZD2281; KU-0059436; CO-CE 42

Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

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

Approximate Solubility: 0.1 mg/mL pH independent solubility across physiologic range

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

Description: crystalline solid

How Supplied: AstraZeneca supplies and the CTEP, DCTD distributes olaparib as green, film-coated tablets in 100 mg and 150 mg strengths.

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

Tablets are packaged in induction-sealed high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle contains 32 tablets with desiccant.

Tablet core components include active drug substance, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black.

Storage: Store in a secure location below 30° C (86° F).

If a storage temperature excursion is identified, promptly return olaparib (AZD2281) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf-life studies are ongoing. Sites are not permitted to re-package tablets. Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.

Route and Method of Administration: Oral. Take tablets without regard to meals.

Potential Drug Interactions: *In vivo* data indicate that CYP3A4/5 is important for olaparib metabolism and clearance in humans. For this reason, avoid concomitant administration of strong and moderate CYP 3A4/5 inducers and inhibitors. Consult the protocol document or study investigator prior to making any dose adjustments related to potential drug-drug interactions.

In vitro data shows olaparib is a substrate for P-glycoprotein (P-gp), but not for organic anion-transporting polypeptides (OATP1B1 and OATP1B3), organic cation transporter 1 (OCT1), multi-drug resistance protein 2 (MRP-2) efflux transporter or breast cancer resistance protein (BCRP). Administration of strong P-gp inhibitors and inducers should be avoided with concurrent olaparib.

Based on *in vitro* data, olaparib inhibits CYP 3A4 and UGT1A1 enzyme systems and induces CYP 1A2, 2B6, and 3A4 and potentially induces CYP 2C9, 2C19 and P-gp. Therefore, avoid concomitant administration of sensitive substrates, particularly those with narrow therapeutic ranges.

Olaparib is also an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and a weak inhibitor of BRCP, but not an inhibitor of OATP1B3 or MRP-2. *In vitro* studies suggest that olaparib may increase exposure of substrates of these transport systems, although the clinical relevance is not clear. The manufacturer recommends that statins, in particular, should be administered with caution when given concomitantly with olaparib.

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

contraceptives may be reduced if co administered with olaparib.

Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should agree to use two (2) highly effective forms of contraception throughout study participation and for at least one (1) month after the last dose of olaparib. It is not known whether olaparib is found in seminal fluid, so as a precaution, male study participants must use a condom during treatment and for three (3) months after the last dose and should avoid fathering a child or donating sperm during this same time period. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

Lactation is a protocol exclusion criterion and not advised since there is potential for serious adverse reactions in breastfed infants. Advise lactating women to not breastfeed during study treatment and for one (1) month after receiving the last dose of olaparib.

Because the adverse events related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery.

There are no data on the effect of olaparib on wound healing, therefore as a precaution, olaparib treatment should be stopped at least 3 days prior to planned surgery. After surgery olaparib can be restarted when the wound has healed. No stoppage of olaparib is required for any needle biopsy procedure.

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

8.1.2 CTEP IND Olaparib (NSC 747856)

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Sites may order olaparib supplies when a patient is enrolled onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.3.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions above IB access may be directed to the PMB IB coordinator via email.

8.1.3.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- IB Coordinator: IBCoordinator@mail.nih.gov

8.2 Commercial Agent

Ramucirumab (CYRAMZA®) is commercially available and will be dosed at 8 mg/kg every 2 weeks as described above, please see the October 2016 FDA-approved package insert for additional details.

Product description: Ramucirumab is a recombinant human IgG1 monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2. Ramucirumab has an approximate molecular weight of 147 kDa. Ramucirumab is produced in genetically engineered mammalian NS0 cells. Ramucirumab is a sterile, preservative-free, clear to slightly opalescent and colorless to slightly yellow solution for intravenous infusion following dilution and preparation.

How supplied: Ramucirumab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-dose vials. Ramucirumab is formulated in glycine (9.98 mg/mL), histidine (0.65 mg/mL), histidine monohydrochloride (1.22 mg/mL), polysorbate 80 (0.1 mg/mL), sodium chloride (4.383 mg/mL), and Water for Injection, USP, pH 6.0.

Storage and handling: Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light. **DO NOT FREEZE OR SHAKE** the vial.

Solution preparation (how the dose is to be prepared):
Inspect vial contents for particulate matter and discoloration prior to dilution. Discard the vial, if particulate matter or discolorations are identified. Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light.
• Calculate the dose and the required volume of ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg/10 mL or 500 mg/50 mL at a concentration of 10 mg/mL solution of ramucirumab.
• Withdraw the required volume of ramucirumab and further dilute with only 0.9% Sodium Chloride Injection in an intravenous infusion container to a final volume of 250 mL. Do not use dextrose containing solutions.
• Gently invert the container to ensure adequate mixing.
• DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.
• Store diluted infusion for no more than 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature (below 25°C [77°F]).
• Discard vial with any unused portion of ramucirumab.

Route of administration: Visually inspect the diluted solution for particulate matter and discoloration prior to administration. If particulate matter or discolorations are identified, discard the solution. Administer diluted ramucirumab infusion via infusion pump over 60 minutes (+/- 15 minutes) through a separate infusion line. Use of a protein sparing 0.22 micron filter is recommended. Flush the line with sterile sodium chloride (0.9%) solution for injection at the end of the infusion.

Prior to each ramucirumab infusion, premedicate all patients with an intravenous histamine H1 antagonist (e.g., diphenhydramine hydrochloride). For patients who have experienced a Grade 1 or 2 infusion-related reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each ramucirumab infusion.

Agent Ordering: Commercially available through Eli Lilly and Company.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Integral Laboratory or Imaging Studies
Not applicable

9.2 Integrated Correlative Studies

9.2.1 BROCA-HR (Integrated Biomarker)
To assess correlation of response and effect of homologous recombination deficiency (HRD) status, the BROCA-HR assay, established by the Swisher laboratory will be applied. In addition to testing the tumors, a blood sample will be obtained at baseline for germline BROCA-HR testing. Somatic BROCA-HR testing will be done using the baseline tumor biopsy tissue on all pre-treatment biopsy specimens. The prevalence of biomarkers and correlation with response will be used to plan subsequent study as described in section 13.

One hypothesis for response to a PARP inhibitor is that cancer cells need to be deficient in homologous repair, but also proficient in the alternative error prone non-homologous end joining DNA repair pathway. Thus, loss of HR is not by itself, sufficient for sensitivity to a PARP inhibitor, and an accurate predictor of responsiveness could require assessment of many components of both the HR and non-homologous end joining pathways. A more efficient assay, which would not require a prior knowledge of the critical elements of these DNA repair pathways, would instead measure DNA repair capacity. Recent evidence suggests that BRCA1/BRCA2 deficient cancers exhibit global DNA alterations termed “genomic scarring” that are consistent with their reliance on non-homologous end joining. This genome scar could serve as a downstream functional output to measure DNA repair capacity, indicative of both HR deficiency and non-homologous end joining proficiency. The BROCA-HR panel will be applied to the tumor samples as an integrated biomarker to evaluate if “genomic scarring” is present in the tumor samples. Additional detail is provided in 2.4.1.

DNA will be extracted from peripheral blood mononuclear cells and FFPE archived tumor tissue containing at least 30% tumor nuclei. A targeted capture and massively parallel sequencing approach called BROCA-HR will be applied to samples. For the proposed study, the most recent version of BROCA-HR panel with 84 genes that serves as a single assay for germline and somatic mutations that influence response to therapy will be utilized. Library preparation has been fully automated to increase sample turnaround and lower cost. Paired-end libraries with 350bp inserts will be prepared from 1 μg of constitutional or neoplastic DNA and hybridize to a custom pool of oligonucleotides targeting genomic regions as previously described using the SureSelectXT enrichment system on a Bravo liquid-handling instrument (Agilent). Following capture, samples will be barcoded with 48 different indexed primers. The pooled samples are sequenced on a single lane of a HiSeq flowcell (Illumina) with 2x101bp paired end reads and a 7bp index read to allow for de-multiplexing and binning of individual samples. Single agent variants and insertions and deletions will be detected as previously described with some updates in the bioinformatics pipeline. Deletions and duplications of exons will be detected by a combination of depth of coverage and split read analysis as previously described, supplemented

with additional alignments generated by SLOPE. All germline loss of function mutations in cancer susceptibility genes will be confirmed with PCR amplification and Sanger sequencing. Cases will be identified as HR proficient or deficient based on sequencing data of known Fanconi anemia (FA)-BRCA genes and then correlate HR proficiency with response to PARPi on the trial.

9.2.1.1 Collection, handling, and shipping of specimens. Details for specimen collection, preparation, and shipping will be outlined in a lab manual that will be provided to the sites. In short, tumor samples will be collected at each study site. Tissue will be formalin-fixed and paraffin embedded. The samples will then be shipped to the Yale STS laboratory for further processing. Slides with cut tumor sections will be shipped from Yale to Dr. Swisher's lab at University of Washington for the analysis described above. In addition, 7ml of blood is required for germline sequencing, which will be shipped to Dr. Swisher's laboratory directly.

9.1.1.2 Site(s) Performing Correlative Study:
Dr. Elizabeth M. Swisher, MD
University of Washington
1959 NE Pacific St
Health Sciences Building K154
Seattle, Washington 98195-6460
Phone: 206-543-3669
swishere@uw.edu

9.3 Exploratory/Ancillary Correlative Studies

9.3.1 Immunoassay for Poly-ADP-Ribosylated (PAR) Substrates

The immunoassay for PAR substrates will be performed on all 16 week post treatment biopsy specimens. The PARP enzyme creates poly-ADP-ribosylated (PAR) molecules, thus an immunoassay was developed to measure PAR as a surrogate for PARP inhibition. Abbot Laboratoies and the NCI-Frederick developed a cross-validated quantitative immunoassay for poly-ADP-ribosylated (PAR) substrate. The assay dynamic range is 31-2000 pg/ml PAR with a lower limit of quantitation of 15 pg/ml PAR. The assay uses high, midrange, and low controls produced from the human melanoma line Colo829. Specimen handling was optimized for both PBMCs and tumor needle biopies (18 gauge), and harmonized for use with the same standard and controls. Specimens could be subjected to at least 3 freeze-thaw cycles without a detectable loss of antigen binding. Assay precision was determined at both Abbott and the NCI-Frederick to be better than 80%. Accuracy, as assessed by spike recovery of pure PAR into peripheral blood mononuclear cell lysates was 100% +/- 20%. Assay dilution linearity was established for the Colo829 controls and tumor lysates, although deviations from linearity are observed in some tumor homogenates, and assay conditions are controlled to compensate for the lack of linearity. The validated assay has been used to measure PAR levels in peripheral blood mononuclear cells in healthy donors, and will be used to measure PAR in peripheral blood mononuclear cells and tumor biopsies in the proposed protocol.

9.3.1.1 Collection of Specimen(s)
9.3.1.2 Handling of Specimens(s)
9.3.1.3 Shipping of Specimen(s)
9.3.1.4 Site Performing Correlative Study:
Dr. Joann Sweasy Laboratory
15 York Street
Hunter Building 308
New Haven, CT 06520
Joann.sweasy@yale.edu
203-785-2981

9.3.2 Signature 3
Collection, Handling, and Shipping of Specimens:

Signature 3 testing will be done on all pre-treatment biopsies for analysis as a potential biomarker. The results of signature 3 testing will be correlated with ORR, and other potential biomarkers including the BROCA-HR panel and signature 3 testing The following description of the biomarker testing for this was prepared at the recommendation of Drs. James Tricoli and Tracy Lively at the NCI, who were consulted about the form this part of the protocol should take. Because much of the DNA-Based Mutation Assay Template does not fit next generation sequencing (NGS) of tumor DNA, they suggested that a separate, full description of the proposed testing be submitted along with a copy of the DNA-Based Mutation Assay Template competed to the extent possible for a study involving NGS.

Whole exome screening of DNA from gastric tumors for the signature 3 mutational pattern will be performed in the Yale Clinical Molecular Pathology Laboratory (YCMP Lab) on tissue microdissected from histologic sections of gastric tumor specimens. These sections will be cut from formalin-fixed, paraffin-embedded (FFPE) blocks and mounted unstained on glass microscope slides. One of the sections adjacent to those cut for microdissection will be stained with hematoxylin and eosin and examined by a pathologist (Dr. Sklar) to assess tumor content, location of the tumor cells within the section, and the extent, if present, of necrosis, hemorrhage, or any other potentially interfering features or conditions. The areas containing concentrated tumor cell populations in the stained slide will be circled and the corresponding regions in the unstained slides manually microdissected with a sterile scalpel blade. In cases for which manual microdissection is not adequate, for instance, due to small clusters of tumor cells distributed within stroma or other non-malignant tissue, laser-capture microdissection will be carried out. The goal for this pre-analytic part of the testing is to obtain, either by manual or laser-capture microdissection, starting material that is enriched for tumor cells to the level of at least 70% tumor. Enrichment of tumor prior to sequencing increases the sensitivity of the sequencing, which will be important because of the reduced read depth inherent in whole exome sequencing (WES).

DNA will be extracted from these tissues using the Qiagen FFPE DNA Tissue Kit. Additionally, normal DNA from the patient will be obtained from buccal swabs or from histologically normal tissue, free of tumor. WES of tumor and normal DNA will be conducted in parallel using the Ion Torrent whole exome platform. Libraries of DNA fragments for sequencing will be constructed

by highly multiplexed PCR of tumor and normal DNA using AmpliSeq Exome primers. Libraries for tumor and normal DNA will be built separately incorporating short oligonucleotide sequences at the end of the fragments to "barcode" the DNA fragments from the two sources. (Since the libraries generated from tumor and normal DNA will be mixed and sequenced together, barcoding is necessary to disambiguate the results for tumor and normal DNA when the sequence results are analyzed.) Input for the initial amplification during library building (18 cycles of PCR) will be 60 ng of genomic tumor DNA and 20 ng of normal DNA (lower for normal DNA because of less need for read depth and analytic sensitivity), distributed among 12 primer pools in 12 different tubes. Amplicons from the library builds will be reamplified and attached to sequencing microbeads in aqueous droplets within water-oil emulsions (all performed using the Ion Chef instrument), such that the great majority of beads are decorated with a pure, clonal population of amplicons. Sequencing of the DNA amplicons on beads will be carried out with P1 v3 sequencing chips (each containing >165 million sensor wells each capable of sequencing amplicons attached to a single bead) on a Proton sequencer, or with Ion 540 chips on a S5 XL sequencer. Both instruments are available in the lab for this project; however, the greater likelihood is that the P1/Proton system will be used because it is cheaper. With highly efficient sequencing chip loading that achieved in the YCMP Lab (occupation of ~90% of wells in the P1 chip), the mean read depth is expected to exceed 200x for the tumor DNA and proportionately lower for the normal control. Using the newer HiQ chemistry, average fragment lengths should be about 250 nucleotides for about 3.2 megabases of total DNA, covering about 98% of the exome.

The raw sequencing results will be aligned to the hg19 reference genome and variants called using Torrent Suite, Ion Reporter, and custom software developed at Yale. Those variants deemed somatic by virtue of their absence from the matched normal DNA of the patient, will be evaluated for signature 3 sequences, using an algorithm designed in house, specifically for this purpose. Mutations in critical genes and a sampling of signature 3 mutations (a sampling only because of the high volume of such mutations expected per case) will be manually checked as a quality control, in addition to review of overall quality metrics produced by Ion Torrent software for each sequencing run.

The Ion Platform system affords a particular advantage relative to Illumina sequencing for the research proposed in this LOI. Ion Torrent has pioneered the use of highly multiplex PCR to select regions of genomic DNA for targeted sequencing (for instance, ~24,,000 amplicons per primer pool to cover the entire exome). This approach generally means that smaller amounts of starting DNA are needed for sequencing, including for WES—a critical consideration when dealing with clinical samples, which often consist of core needle biopsy or aspiration specimens that must also be utilized for a variety of diagnostic tests and analyses. The theoretical disadvantage of Ion Torrent is lower throughput. To increase read depth and horizontal coverage across the exome, an entire sequencing chip will be used for each case (tumor plus paired normal control from the same patient). Illumina flow cells accommodate more cases per run, but this difference is negated by the fact that cases for the proposed trial will come in one at a time and batching will not be possible, to achieve a turnaround time for returning sequencing results within 10 days of receipt of the specimen in the YCMP Lab, which is the intent for biomarker analysis in this trial. Both Illumina and Ion Torrent sequencing are associated with systematic sequencing errors—Illumina related to CG-rich regions and Ion Torrent related to

homopolymeric regions of sequence. The YCMP Lab has extensive experience with the bioinformatics to interpret Ion Torrent sequencing and the identification of artifacts, both through the development out of the Yale Tumor Profiling Lab (see below), from which the YCMP Lab was spun off, and through the NCI-MATCH trial for which the YCMP Lab is one of the four national sequencing centers. Furthermore, the parallel sequencing of normal paired DNA permits discrimination and elimination of many of these artifacts encountered with Ion Torrent sequencing.

Validation for feasibility, clinical sensitivity, specificity, limit of detection, reproducibility, and fit for purpose will be carried out using control samples that are available to the YCMP Lab from the Yale Tumor Profiling Lab, which was founded by Dr. Sklar six years ago, and performs routine clinical NGS of tumor DNA using a variety of gene panels, including a 409-gene panel that contains analyzes most known cancer-related genes. Among the cases that have been sequenced and are available as controls, are a sizable number that contain verified *BRCA1/2* mutations or lack mutations in *BRCA1/2* and other genes in the homologous repair pathway. DNA samples from cases that have been previously analyzed by WES are also available, as are DNA from cell lines that have been previously subjected to WES.

Feasibiilty testing will carried out on six cases of FFPE tissue with known sequences. The primary purpose of this activity will be to insure that the coverage and depth of sequencing described above can be achieved on a routine basis.

Following feasibility testing, validation for clinical sensitivity will be performed on 20 DNA samples. The vast number of potential variants that are possible within the human genome presents a problem for validation of biomarker detection by NGS, compared, for instance, to validation of a single variant or small set of variants located within one or two genes. We will take two approaches to this problem. One will be to sequence the DNA from 12 FFPE samples (preferably gastric carcinomas), the DNA of which has either been large gene panel sequenced or undergone WES. We will select these cases to contain a variety of different types of mutations: single nucleotide variants (SNVs), small insertions and deletions (indels, ≤4 basepairs), larger indels (>4 basepairs), and gene amplifications. However, for this validation and trial, the most relevant variants will be SNVs because signature 3 mutations represent a subset of SNVs. Additionally, six of the FFPE cases will be ones that contain mutations of *BRCA1* or *2*, both to confirm that mutations in these genes can be detected in FFPE tissues and that the signature 3 pattern of mutation normally associated with mutations of BRCA1/2 can be accurately discerned.

The second approach will be to perform WES on DNA of eight from established HAPmap cell lines in which all single nucleotide polymorphisms (SNPs) have been determined previously and are available from commercial and other sources. Some of them have been used in the NCI-MATCH sequencing validations and are already in the lab. These cells lines will be prepared as cell pellets, fixed in 10% buffered formalin, and embedded in paraffin, to simulate FFPE tissue. The rationale for using HAPmap cell lines is to evaluate the sequencing system being utilized as efficiently and thoroughly as possible for its ability to detect variants throughout the exome.

Validation for specificity will be combined with sensitivity testing to show that false negative variants are detected at a minimum in the 20 samples studied for clinical sensitivity by WES. A

sampling of apparent false negative variants that cannot be eliminated by adjusting bioinformatics filters used in variant calling will be analyzed by Sanger sequencing to resolve the ambiguity and help to establish the true rate of false negative results.

Limit of detection will be performed by performing WES on serially diluting four FFPE DNA samples into HAPmap DNA (e.g., 50%, 25%, 12.5%, 6.25%, and 3.12%) to determine the lowest concentration at which confirmed variants within the FFPE DNA can still be detected. The expected level is 5-10%, given the mean average read depth of 200x.

Validation of reproducibility will be conducted by performing WES three times each on DNA four FFPE samples to determine whether each sequence analysis produces the same results. These three repetitions will be performed on different days, which is required due to the capacity of the Proton sequencer, but also serves as a truer test of reproducibility. Additionally, over the course of the trial, DNA from the same HAPmap sample will be analyzed after every twentieth case to check for continued reproducibility.

Fit for purpose validation of the entire biomarker workflow will be carried out by having two centers other than Yale mail samples to the YCMP lab and performing WES to insure that samples can be processed efficiently within the 10-day window. Optimally, we will try to have this performed on samples that have been extensively sequenced elsewhere. Alternatively, we can mail to ourselves samples from which the DNA has previously been sequenced at Yale.

Please also see the NCI template for "DNA-based Mutation Assays" and the "Standard Operating Procedures" for WES by the Yale Clinical Molecular Pathology Laboratory, which are provided as separate documents.

Site Performing Correlative Study:
Dr. Jeffrey Sklar in the Yale Molecular Pathology Lab
PO Box 208023
310 Cedar St. LH 215
New Haven CT 06520
203-785 4492

9.3.3 Genomic assay for "BRCAness"

Through our involvement in the PanCancer genomics project, we have direct access to the combined germline and somatic data form 3,299 TCGA tumors from 12 cancer types [80] [81] . These are exome data derived from TCGA. Approximately 150 of these exomes are form germline carriers of mutant BRCA 1/2 alleles. Since our goal is to build a diagnostic test that can identify not only germline variants in BRCA family genes, but to also identify genomic scarring based on LOH/HRD we need a test with sufficient coverage to do both. We will run three algorithms on the TCGA germline BRCA 1/2 deficient and disease-matched controls: The number of telomeric allelic imbalances (NtAI), large scale transition (LST), and homologous recombination deficiency score (HRD-LOH) [82-84].

We will run all three assays on SNP data from the aforementioned 300 case / control sets and

assess diagnostic sensitivity, specificity and accuracy, using germline BRCA status as the gold standard. AUC curves will be calculated and the top performing test(s) will then be brought forward first to the down sampling set, described below.

The most ideal scenario would be if we had enough sequence data in the panels that we use for allocation to clinical trials, such as that conduced herein. This trial will use the BROCA-HR panel, and whole exome sequencing data will be available for the signature 3 correlative analysis. We will then rerun the NTAI, LST, and HRD-LOH assays described above using the down sampled exome data as the input.

AUC curves will be calculated and the top performing test(s) will then be validated by analyzing archival cases of gastric cancer available through the UCSF HDFCCC Tissue Core. DNA extracted from tissue samples will be analyzed for the HR defect signature identified through the work described above and mutations in the BRCAness-associated genes identified by us (BRCA1, BRCA2, ATM, ATR, PTEN, PARP1, MRE11A, PALB2, CDK12, BAP1, PRKDC, BARD1, BACH1, FANCD2, FANCE, CHEK1, CHEK2, PMS2, FANCA, FANCC, FANCF, XPA, NBN, BLM, BRIP1, RAD51B, RAD51C, RAD51D, and RAD50) by next generation DNA sequence analysis using a capture approach and the Illumina Myseq instrument (available at the UCSF Gladstone Genomics Core). Subsequently, the signature will be applied in a systematic manner to the data produced in the clinical trial with one of these assays. The validation studies will be performed in Dr. Ashworth' laboratory at UCSF. Prior work in gastric cancer estimates that around 20% of samples will score in the upper quartile of all three of these assays [85]. These estimates will then be available for further analysis such as supervised analytics looking at response to PARP, platinum, and other clinically observed characteristics.

Expected results: This aim will determine the applicability of clinically deployed sub-exome sequencing panels for the assessment of BRCAness using genomic measurements.

Pitfalls/alternative approaches: It is possible that the DNA footprint generated by the commercial assays fails to reliably detect BRCANess in TCGA exomes. In particular, the NtAI may not perform well because it requires telomeric sequences, which are not well captured on sub-exome panels. If this were the case, and further funding were obtained we could begin work on building a targeted addition to these tests, but that would increase costs and not be ideal for large population screening at major cancer centers.

Site(s) Performing Correlative Study:
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Box 1705, UCSF
San Francisco, CA 94143-1705
Michael.Korn@ucsf.edu

9.3.4 Factors demonstrating synthetic lethality with PARP inhibitors in gastric cancers.

Aim 1. *Elucidating the role of key signal transduction processes in mediating responsiveness to PARP inhibitors in gastric cancer.* We will expand our panel of gastric cancer cell lines to a total

of 20 cell lines. These lines that are genomically well characterized as part of the Cancer Cell Line Encyclopedia (Broad Institute). Cell lines will be selected harboring mutations conferring BRCAness and to represent chromosomally instable and mismatch repair deficient subtypes of gastric cancer. We will profile cell lines for their responsiveness to DNA damaging agents and PARP inhibitors, either alone or in combination. These include bleomycin (a direct inducer of DNA double-strand breaks) and cisplatin as well as temozolomide (both indirect inducers of DNA double-strand breaks). Cell lines will be treated with bleomycin (100 μg/ml), cisplatin (5 μM) or temozolomide (200 μg/ml) or PARP inhibitors (olaparib, talazoparib or rucaparib; all compounds are available at the Ashworth and Korn labs from commercial sources) for up to 5 days and analyzed for cell viability (Cell TiterGlo assay), alterations in cell cycle distribution, and apoptosis (fluorescence activated cell sorting, FACS). To assess the extent of DNA damage we will measure intra-nuclear γH2AX focus formation by confocal microscopy. Cells will be grown and treated on cover-slips in 6-well dishes and, after fixation, stained using a rabbit anti-γH2AX antibody. The number of foci in at least 100 cells per cover slip will be determined. To assess PARP activity, poly-ADOP-ribolyzation will be determined using a chemiluminescence detection approach (Universal Chemiluminescent PARP Assay Kit, Trevigen). Based on the results of this initial screen, a subset of cells with low and high DNA repair response to DNA damaging agents as well as low and high sensitivity to PARP inhibitors will be selected. Cells will be treated with increasing doses of inhibitors of key oncogenic pathways, including PI3K (BKM120, BYL719), RAF-MEK-ERK (GSK1120212, PD-0325901), TGFβ (LY2157299), WNT (PRI-724), Notch (LY-3039478), Hedghog (vismodegib), JAK-STAT (ruxolitinib). Based on these results of this initial screening, drug combinations will be tested. For example ,if we reproduce down-regulation of DNA repair activity by PI3 kinase inhibitors, we will assess efficacy of these inhibitors in combination with PARP inhibitors +/- DNA damaging agents.

Aim 2. *Unbiased identification of modifiers of responsiveness to PARP inhibitors.* We will utilize a pooled shRNA library (DECIPHER, Cellecta) to identify potential modifiers of response to PARP inhibitors. The library contains 27,500 sHRNAs targeting 5,046 signaling components. We will select gastric cancer cell lines with intermediate sensitivity to the highly potent and selective PARP inhibitor talazoparib based on the results obtained in Aim 2A. Cells will be infected with lentiviruses expressing the sHRNA library and subjected to selection. Subsequently, cells will be treated with talazoparib or with vehicle control. Abundance of each barcoded hairpin will be quantified to identify shRNAs that were selectively depleted during treatment with talazoparib, but not vehicle. TO assess the total population of transduced shRNAs for control purposes, genomic DNA will also be isolated and shRNAs identified from cells just after transduction but before drug treatment. Analysis of abundance shRNA species, next-generation DNA sequencing will be utilized in collaboration with the UCSF Genome Analysis Core. Hits will be validated experimentally using multiple shRNA species or specific inhibitors if available.

Aim 3. *Establishment of PDX tumors from patient samples and assessment of target inhibition and efficacy of novel drug combinations involving PARP inhibitors.* Fresh biopsies will be obtained from selected patients, and on repeat biopsy at 16 weeks for eligible patients. We will aim at capturing tumors harboring a diverse spectrum of mutations conferring BRCAness. We will rest target inhibition and efficacy of novel combination therapies in these PDX models. Based on our preliminary data, we expect that this will include a combination of MEK and

PARP inhibitors. Before testing this combination or new combination resulting from the work in aims 1 and 2, in mice harboring xenograft tumors, we will assess treatment toxicity in NOD scid mice. Groups of three mice will be treated with solvent (DMSO), single inhibitors (e.g. talazoparib or PD0325901), or the combination of both at three different dose levels. In the case of talazoparib and PD0325901, mice will be treated at dose levels 0.1, 0.22, and 0.33 mg/kg of talazoparib and 5, 7.5, and 10 mg/kg of PD0325901 resulting in a 4 x 4 matrix requiring 32 mice per study. The maximum doses of both inhibitors that can be administered without occurrence of severe toxicity will be chosen for subsequent studies. We will then proceed with pharmacodynamics studies to validate target inhibition by the PARP and MEK inhibitor combination in the PDX models. Per individual tumor model, subcutaneous tumors will be generated in 6 mice and allowed to grow to a volume of 300 mm^3. Animals will be dosed with the compounds (for example talazoparib and PD0325901) or vehicle control buffer for three days at doses that were found to be safe in the toxicity studies. Animals will be sacrificed for hours following the last drug administration. Tumors and adjacent normal tissue will be harvested and snap-frozen in liquid nitrogen or fixed in buffered formalin. Proteins will be extracted from frozen tissues using protocols established at our laboratory. Phosphorylation of effector proteins, including pERK, pAKT, and pPRAS40 will be determined by quantitative Western blot analysis using fluorescence based imaging system (Odyssey, Licor). PARP inhibition will be assessed using the PARP in vivo PD Assay II kit (Trevigen). If no evidence of target inhibition is observed in any model for a given inhibitor, the respective experiment will be repeated at a modified dose based on the toxicity study. Otherwise, apoptosis induction will be evaluated by TUNEL assay. A Student t-test will be used to determine statistical significance of differences between treated and control groups. Efficacy studies in primary PDA xenograft tumors will also be conducted. Having established optimal doses for efficient target inhibition, we plan efficacy studies in the selected PDX models. Endpoints for these studies will be tumor response rate and overall survival. Tumor size will be calculated with biweekly caliper measurements. Compounds will be administered daily by oral lavage. Experiments will be terminated on day 28 or when any tumor exceeds 1,500 mm^3 in greatest dimension. Relative tumor growth inhibition (TGI) will be calculated by relative tumor growth of treated mice (T) divided by relative tumor growth of control mice I or (T/C). We will use the following definitions: Response = 0-20% TGI; Stable disease = 21% to 50% TGI; Tumor progression ≥50% TGI. Per study, there will be four cohorts treated with control (i.e. DMSO), single agents (for example talazoparib and PD0235901), and drug combination. We will enroll 8 tumor bearing mice per treatment group. With this sample size and using a 1-sided t-test, we can detect a 33% or greater growth inhibition with 80% power at a 5% level of significance. Experiments will be repeated once. Differences in response rates will be determined using Satterwaite's t-test (unequal variances) with 1-sided 5% Type I error. Kaplan-Meier survival data will be analyzed using a log rank test.

Pitfalls/alterative approaches: The proposed experiments are likely to reveal new mechanisms involved in DNA homologous recombination repair that can be exploited therapeutically. Our findings related to the interaction of the RAF-MEK-ERK pathway and PARP inhibitors sensitivity are an example of successful application of the candidate pathway approach. However, the pathways of interest are highly interconnected. Based on the findings of the experiments described, we might expand mechanistic analysis to be able to interpret findings. In such case we will utilize Reverse Phase Protein Lysate Array technology as we have done before. We expect that CRISPR analysis will be technically feasible and reveal new regulators of

HR repair. The technology is established in the Ashworth lab. If technical challenges are encountered, we will collarboarte with Drs. Kampmann and Weissman at UCSF who invented the technology. The team at Memorial Sloan Kettering Cancer Center has extensive experience with establishing PDX models and we don't expect any problems with this part of the aim.

Sites Performing Correlative Study:
Dr. Michael Korn (UCSF) and Dr. Yelena Janjigian (Memorial Sloan Kettering)
Box 1705, UCSF
San Francisco, CA 94143-1705
Michael.Korn@ucsf.edu

9.3.5 T Cell Receptor Diversity.

By using next generation sequencing of TCRβ repertoire, Dr. Fong's lab has demonstrated that maintenance of pre-existing high-frequency clonotypes is associated with clinical response and improved overall survival following ipilimumab [79]. Using these established methods, we will determine the T cell clonotypes in blood of clinical trial patients obtained pre- and post-treatment. Repertoire diversity will be measured using Shannon's and clonality [86, 87]. Repertoire change between serial timepoints will be measured using Morisita's distance, which is not significantly influence by sample size [88, 89]. Numbers will be reported as distances with 1 indicating maximal dissimilarity. Paired t test will be applied to each diversity metric comparing pre-and post-treatment to test if there is a significant treatment effect. Two-sample Wilcoxon rank sum test will be utilized to compare the clonality index at each time point between patients with and without BRCAness. All analyses will be done by statistical software. Statistical significance will be declared at an alpha level of 0.05, and no adjustment will be made for multiple comparisons unless noted. Identification of differentially abundant clonotypes pre and post-treatment for each sample will be performed using a DESeq R package modified to account for normal variation in the repertoire over time and to compensate for the lack of replicates in the experimental design. Multiple testing adjustments will be accomplished by controlling FDR for each sample. Downstream analysis will be applied to those significant clone to see if multiple T cell clonotypes with different nucleotide sequences may converge upon the same amino acid sequence, which would be consistent with antigen selection.

Where available, comparisons of TCR transcript frequency and repertoire diversity (Shannon's and clonality indices) will be made between pre- and post-treatment biopsies by paired Wilcoxon rank sum test. At an alpha level of 0.05, 20 samples would ensure 80% power to detect effect size of 0.66 in repertoire diversity to declare that there is a significant difference in TCR frequency between pre- and post-treatment biopsies. We also plan to compare biopsies from patients with and without BRCAness.

We routinely test PBMC processed in our laboratory for HLA-A2 expression. For patients who possess this HLA allele (approximately 40% of UCSF patients) and are known to have HPV+ tumors, we use MHC-peptide tetramers, specific for HPV derived epitopes (Beckman Coulter, Brea, CA) to FACS sort HPV reactive CD8 T cells. These sorted T cells will also be subjected to TCR sequencing. We will then use the clone-specific sequences to track these antigen-reactive T cells in both the blood and tissue with established methodologies [79].

Pitfalls/alternative approaches: As we have seen in pancreatic adenocarcinoma, BRCA2 carreirs can possess a higher number of neoepitopes. We anticipate that patients with the highest neoepitope burden (e.g. with BRCAness phenotype) will have a lower clonality indices (i.e. greater TCR diversity) in both the blood and the tumors. The tetramer sorting experiments will allow us to determine the relative contribution of virus-specific T cells to the modulated immune responses with PARPi. However, the circulating T cell repertoire may not reflect what is going on in the tumors. Our approach will allow us to determine whether the TCR repertoire in the blood can serve as a surrogate for the TCR repertoire in the tumor. We may find that a high neoantigen burden could actually lead to increased clonality (i.e. decreased diversity) in tumors due to focusing of the immune response to these immunodominant epitopes. Nevertheless our approach will be able to assess for this alternative hypothesis. We do not anticipate any difficulties in performing these assays. These results would lay rationale for combinations with immunotherapy in the future.

Site(s) Performing Correlative Study:
Dr. Michael Korn (UCSF)
Box 1705, UCSF
San Francisco, CA 94143-1705
Michael.Korn@ucsf.edu

9.3.6 Circulating Tumor DNA (Exploratory Correlative).

Peripheral blood will be placed in a biorepository for assessment of circulating tumor DNA and molecular profiling at a later date.

9.3.6.1 Specimen Receipt and Processing at the EET Biobank

Plasma specimens will be transferred to the EET Biobank for extraction of cfDNA.

9.3.6.2 Site Performing Correlative Study

Circulating Tumor DNA will be performed by the NCLN Genomics Laboratory under the direction of Mickey Williams, Ph. D.

9.3.6.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:
NCLN Genomics Laboratory at The University of Texas MD Anderson Cancer Center
6565 MD Anderson Blvd
Suite 3.4019
Houston, TX 77030
Attn: CTO, NCLN Lab, Jincy Veliyathu or Khushali Rajendra Patel

9.3.6.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes, NCLNGenomicsReceiving@nih.gov

10. STUDY CALENDAR

Phase 1 and Phase 2:
Baseline evaluations are to be conducted within the 28-day screening period. CT scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study[11]	Cycle 1 (±2 days)		Cycle 2 (±2 days)		Cycle 3 (±2 days)		Cycle 4 (±2 days)		Cycles 5 – 7 (±2 days)		Cycle 8 and later (±2 days)		Follow up[5]
Day		1	8	1	8	1	8	1	8	1	8	1	8	
Olaparib		A----------→												
Ramucirumab[13]		B		B		B		B		B		B		
Informed consent	X[11]													
BROCA-HR Testing	X													
Pre-treatment Biopsy[1]	X[1]													
On-treatment Biopsy[2]												X[2]		
Research blood for biobank	X	X	X	X		X		X		X		X		X
Demographics	X													
Medical history	X													
Adverse Event Evaluation	X	X	X	X		X		X		X		X		X
Physical exam	X	X		X		X		X		X		X		X
Vital signs	X	X		X		X		X		X		X		X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
INR and PTT	X													
CBC w/diff, plts	X	X	X	X		X		X		X		X		X
Serum chemistry[3]	X	X	X	X		X		X		X		X		X
Buccal swab	X													
TSH[10]	X									X[10]				
Urinalysis[8]	X	X		X		X		X		X		X		
EKG [9]	X													
Tumor measurements[12,14]	X	Tumor measurements are repeated every *6-weeks ± 7 days*[14]. Documentation (radiologic) must be provided for patients removed from study for progressive disease. Imaging should include chest, abdomen, and pelvis.												X[7]
Radiologic evaluation[12,14]	X	Radiologic measurements should be performed every *6-weeks ± 7 days*[14] for the duration of enrollment. Imaging should include chest, abdomen, and pelvis.												X[7]
B-HCG	X[4]	X												
ECHO (if indicated)	X[6]													

A: Olaparib: Dose as assigned; *administration schedule*
B: Ramucirumab: Dose as assigned*; administration schedule*
1: Mandatory for all patients in both phases of study between 3 – 28 days before day 1 of treatment.
2: Optional for all patients if felt to be safe in the opinion of the investigator. The on treatment biopsy should be obtained between days 3 – 11 of cycle 8 (week 16).
3: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [50], sodium, magnesium, and GGT.
4: Serum pregnancy test (women of childbearing potential) one test 28 days prior to starting treatment. Day 1 serum pregnancy test should be prior to starting treatment.
5: Off-study evaluation: 4 weeks after coming off study. Patients will continue to be evaluated for survival every 3 months.
6: Prior treatment with anthracyclines, prior treatment with trastuzumab, NYHA classification of II controlled with treatment (see Appendix B), prior central thoracic radiation, history of myocardial infarction within the prior 12 months, prior history of impaired cardiac function.
7: For patients who discontinue the study treatment for reasons other than disease progression will continue to undergo restaging scans every 6 weeks ± 7 days or earlier if clinically indicated, until the documentation of disease progression (see section 5.6 for duration of follow up).
8: Full urinalysis at screening, a urine dipstick protein level may substitute for a full urinalysis for on treatment visits although a full urinalysis may be done if clinically indicated.
9: Within 7 days prior to starting treatment and when clinically indicated.
10: TSH monitoring should be done every 12 weeks or as indicated.
11. The screening period is 28 days and patients must start day 1 of treatment within 28 days of signing consent.
12 Radiologic evaluations should include the chest, abdomen, and pelvis. When appropriate, additional sites of imaging may be applicable depending on disease extent.
13. Ramucirumab should be run over 60 minutes (+/- 15 minutes).
14. Patients that remain on treatment for > 6 months may decrease the response assessment scan interval to every 12 weeks (+/- 7 days) at the discretion of the investigator.

11. MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every week for the first 3 weeks, then every 2 weeks thereafter. In addition to a baseline scan, confirmatory scans will also be obtained ever 6 weeks following initial documentation of an objective response. Patients on treatment for > 6 months may decrease the response assessment interval to every 12 weeks (+/- 7 days) at the discretion of the investigator.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every ever 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 6 weeks following initial documentation of objective response. Patients on treatment for > 6 months may decrease the response assessment interval to every 12 weeks (+/- 7 days) at the discretion of the investigator.

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.

11.1.1 Definitions

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

Evaluable for objective response. All patients who receive treatment will be counted for response rate evaluation. 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.

11.1.2 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.

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.

11.1.3 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 Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*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 which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 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.

11.1.4.2 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).

11.1.4.3 Evaluation of Best Overall Response

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

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

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

	PD/not evaluated			
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Confirmation will be obtained at the regularly scheduled interval of every 6 weeks for study patients and for patients who come off study for reasons other than disease progression.
*** 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

11.1.5 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.

11.1.6 Progression-Free Survival

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

11.1.7 Response Review

Radiology assessments for Yale site will be provided by the Yale tumor metric core. Assessment for other participating sites should be performed per the site's own tumor metric core.

12. STUDY OVERSIGHT AND 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).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the 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). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring

plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or Participating Organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each

ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5 Genomic Data Sharing Plan

Investigators will submit large-scale human genomic data and relevant associated tissue to an NIH-designated data repository in a timely manner. Investigators will also submit any information necessary to interpret the submitted genomic data, such as study protocols, data instruments, and survey tools. The NIH will release data submitted to NIH-designated data repositories no later than 6 months after the initial data submission begins, or at the time of acceptance of the first publication, whichever comes first.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a phase 1 and 2 open-label single arm clinical trial with no randomization of olaparib with ramucirumab for patients with metastatic gastric and gastroesophageal junction adenocarcinoma who have failed at least one prior line of chemotherapy. The study has a phase 1 dose escalation lead in phase for olaparib with standard dose ramucirumab. The primary objective of phase 1 is to determine the safe dose of olaparib with ramucirumab. Olaparib will be

increased up to 300 mg twice daily in tablet dosing. Based on published toxicity profiles for olaparib and ramucirumab outlined in section 5.2 the probability of DLT is in the range of 0.15 to 0.25. The primary objective of phase 2 is to measure the efficacy for olaparib plus ramucirumab by objective response rate (ORR). In phase 2, 40 patients will be enrolled as a pilot study to help determine the foundation for a biomarker stratification design in a larger study. Incidence rates for the BROCA-HR biomarker will be measured in all enrolled patients for both stages. If the incidence rate of the BROCA-HR biomarker is too low (<10%) or efficacy is seen it is unlikely we would not proceed to a larger study. The historical control for ramucirumab monotherapy is an ORR of 3%, and we will assume a null hypothesis of 5%.

Primary Endpoints:
Phase 1: Dose limiting toxicity for olaparib in combination with ramucirumab and the maximum tolerated dose (or the maximum safe dose).
Phase 2: Objective response rate by RECIST v1.1 criteria for combined therapy with olaparib and ramucirumab.

Analytic Plan for Primary Endpoints:
Phase 1: A 3+3 dose escalating approach will be used to determine what dose is the safe dose and should be used in the Phase 2 portion of the study.

Phase 2: Because we do not know the true distribution of our biomarker we will proceed with this 40 patient pilot study to help plan a larger study based on both our observed biomarker prevalence and our response rates. If response rates are observed regardless of biomarker status the subsequent study may not be biomarker driven or an alternative biomarker may be used. Based on published data in the COSMIC and TCGA databases we expect the genes characteristic for HRD in the BROCA-HR biomarker to be positive in approximately 35% of cases. These genes are: ATM, ATR, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, MRE11A, NBN, PALB2, RAD51, RAD51C, RAD51D, RBBP8, SLX4, XRCC2, CDK12. Based on the proposed prevalence of these genes we will enroll to 40 patients and proceed as follows:

Sample Size Justification:

1. If there are 6 or more BROCA-HR+ patients (34 or less BROCA-HR- patients): If there are no responses in BROCA-HR+ patients and no response in BROCA-HR- patients, then it is unlikely we will proceed to a larger study with this combination.
    - For BROCA-HR+ patients: the probability of ≥ 1 responses is > 80% if the true response rate ≥ 25%
    - For BROCA-HR- patients: The probability of ≥ 1 response is > 99% if the true response rate is ≥ 20% and the probability of ≥ 1 response of 80% if the true response rate is ≥ 5%.

2. If there are 6 or more BROCA-HR+ patients (34 or fewer BROCA-HR-): For BROCA-HR- patients, the study will require at least 4 responses for success if we have at least 26 BROCA-HR- patients (65% incidence rate). The probability of 4 responses is 80% if the true response rate is 20%. The study will require at least 3

responses for success if we have at least 20 BROCA-HR- patients (50% incidence rate) the probability of ≥ 3 responses = 80% if the true response rate = 20%. It is very unlikely the incidence rate of BROCA-HR- will be less than 50%.

3. If there are less than 6 BROCA-HR+ patients (35 or more BROCA-HR- patients): If no responses are observed in either cohort, then it is unlikely we will proceed to a larger study with this combination. The probability of ≥ 6 BROCA-HR+ patients is > 85% if the true incidence of BROCA-HR+ is ≥ 20%. The probability of ≥ 6 BROCA-HR+ patients is > 99% if the true incidence rate of BROCA-HR+ is ≥ 35%.

Based upon the results in the above scenarios we will discuss with CTEP on the plan to proceed to a larger study.

Analysis Plan:

The objective response is defined as a complete or partial response, as determined by investigator assessment using RECIST v 1.1 and confirmed by repeated assessment > 4 weeks after initial documentation. Patients with missing or no response assessments are classified as non-responders. The ORR will be estimated using the 95% confidence interval (CI) based on Wilson's method. A 5% 2-sided alpha will be used.

The Wilcoxon rank sum test and Fisher's exact test will be applied to study the association between the response status and the continuous and categorical variables, respectively. The generalized non-linear model and logistic regression will be applied for multivariable data analysis. The adjusted p-value and 95% CI of the odds ration (OR) will be reported.

For the PAR assay and PDX generation involving biopsy samples, the findings will be primarily hypothesis generating and will use descriptive statistics. In addition, with the proposed sample size of 20, the half-width of the 90% CI will be less than 20% with respect to the binary endpoint. It has at least 85% power to detect a correlation coefficient > 0.5 with one-side type I error = 10% with respect to the continuous endpoint.

13.2 Sample Size/Accrual Rate

Planned sample size Phase I: 6 patients
Planned sample size Phase II: 40 patients
Accrual Rate: 10/month

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	2	2	0	0	**4**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	5	4	0	0	**9**
White	16	15	3	2	**36**
More Than One Race	0	0	0	0	**0**
Total	**23**	**21**	**3**	**2**	**49**

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13.3 Stratification Factors

The patients will not be stratified by mutational status, and all biomarkers are either integrated or exploratory. Subset analysis of primary, secondary, and exploratory endpoints will also be performed based on the presence or absence of the integrated biomarkers.

13.4 Analysis of Secondary Endpoints

Analytic Plan for Secondary Endpoints:

- For lifetime data analysis, e.g., progression free survival and overall survival, the BROCA-HR status will be compared for duration of response survival with Kaplan-Meier estimates and log-rank tests. The Rothman confidence interval (CI), which is based on Greenwood's variance, Thomas and Grunkemeier CI, and the simultaneous confidence bands by Nair and Hall and Wellner, will be reported. In addition, the possible risk factors will be compared for survival with log-rank test. For multivariate analysis, the proportional hazards Cox model will be applied to investigate potential prognostic factors, such as age and stage of disease of the PFS data. The adjusted p-values of the hazard ratios and the adjusted 95% confidence interval will be reported.

- Toxicity rates will be tabulated by type and grade and compared to established rates for ramucirumab monotherapy. Ninety-five percent confidence intervals will be calculated for each of these.

Analytic Plan for Exploratory Endpoints:

- The association of BROCA HR assay with Signature 3 will be assessed using a series of contingency table analyses. For instance, we can examine the association of the presence of an individual mutation from the BROCA HR panel with the signature 3 (yes/no) using Fisher's exact test. Next, using a Cochran Mantel Haenzel test we can examine the relationship across the measures. Finally, we wish to examine the relationship of each of these measures with response. To do this multiple logistic regression models can be fit with the response (CR/PR vs SD/PD) considered as the outcome variable and the 3 assay measures can be used predictors. This model can include interactions among the assays. Additional covariates including patient level characteristics (age, gender) and group can be included in these models. These analyses are exploratory therefore no formal adjustment for multiple comparisons will be performed, however it is understood that these tests will be considered hypothesis generating primarily.

- Tumor cells for PDX model, and biobanked tumor tissue and peripheral blood will be used for future studies.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

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

13.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be

performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B: NEW YORK HEART ASSOCIATION CLASSIFICATIONS

Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to Work**
I	None	None	None	Full Time
II	Only Moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician
** At accustomed occupation or usual tasks

APPENDIX C PILL DIARY FOR OLAPARIB

Today's Date _____ Cycle # _____

Patient Name _____ Patient Study ID _____

1. Complete one form for each cycle (14 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.

The first row in the table below is an **EXAMPLE ROW** for how to complete this diary.

OLAPARIB

Take _____ (number) _____ mg tablets twice a day 12 hours apart with or without food. You should avoid grapefruit, grapefruit juice, and Seville oranges while on study because of their affects on the metabolism of olaparib.

Day	Date	100 mg	150 mg	AM	PM	Comments
1	1/1/17	2	0	8:00	8:00	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						

APPENDIX D PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, olaparib. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Olaparib interacts with certain specific enzymes in the liver and can effect the ability to process other medications, and other medications can affect the ability of your body to process olaparib.

Olaparib interacts with a certain specific enzyme in your liver called CYP 3A4 isoenzymes. The drug itself induces the CYP3A4 isozymes, and olaparib is broken down by this enzyme and will be affected by other drugs that inhibit or induce this enzyme.

Olaparib may also interact with P-glycoprotein, organic anion-transporting polypeptide (OATPB1), organic cation transporter 1 and 2 (OCT1 and OCT2), OAT3, multi-drug and toxin extrusion proteins (MATE1 and MATE2K), and BRCP. Administration of strong inhibitors and inducers of these proteins should be avoided while on olaparib. The manufacturer recommends that statins, in particular, should be administered with caution when given concomitantly with olaparib.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

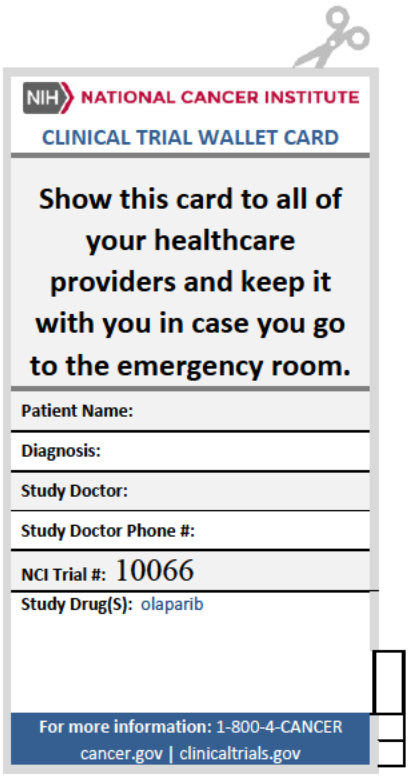
Olaparib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. Avoid ingesting grapefruit, grapefruit juice, Seville oranges, and Seville orange juice while taking olaparib. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Olaparib must be used very carefully with other medicines that use liver enzymes. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP 3A4 isoenzyme.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: 10066

Study Drug(S): olaparib

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX E DIARRHEA MANAGEMENT

Information for patients and caregivers for the management of diarrhea:

- You should take Imodium 4 mg at the onset of diarrhea.
- If diarrhea persists, you should then take 2 mg every 2 hours with each additional bowel movement. No more than 16 mg of Imodium should be consumed in a 24-hour period.
- If you develop more than 4 episodes of diarrhea in 24 hours you should call your study doctor.