

NRG-GY004

(*ClinicalTrials.gov* NCT #02446600)

A Phase III study comparing single-agent olaparib or the combination of cediranib and olaparib to standard platinum-based chemotherapy in women with recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer
NCI Version Date: 08/15/2019

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI).

Lead Organization: NRG / NRG Oncology

<p>Participating Organizations ALLIANCE / Alliance for Clinical Trials in Oncology ECOG-ACRIN / ECOG-ACRIN Cancer Research Group SWOG / SWOG CCTG / Canadian Cancer Trials Group Please see Appendix XV for Japan</p>
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Protocol Agent

<u>Agent</u>	<u>Supply</u>	<u>NSC #</u>	<u>IND #</u>	<u>IND Sponsor</u>
Cediranib	CTEP	732208		DCTD, NCI
Olaparib	CTEP	747856		DCTD, NCI

Participating Sites

- U.S.
- Canada
- Approved International Member Sites

Document History

	Version/Update Date	Broadcast Date
Closure		
Amendment 11	August 15, 2019	
Amendment 10	January 15, 2019	

Amendment 9	August 13, 2018	
Amendment 8	July 23, 2018	
Amendment 7	June 22, 2018	
Amendment 6	January 16, 2018	May 21, 2018
Amendment 5	October 2, 2017	October 17, 2017
Amendment 4	May 30, 2017	July 31, 2017
Amendment 3	March 28, 2017	April 24, 2017
Amendment 2	January 3, 2017	January 17, 2017
Amendment 1	August 12, 2016	November 7, 2016
Activation	November 5, 2015	February 4, 2016

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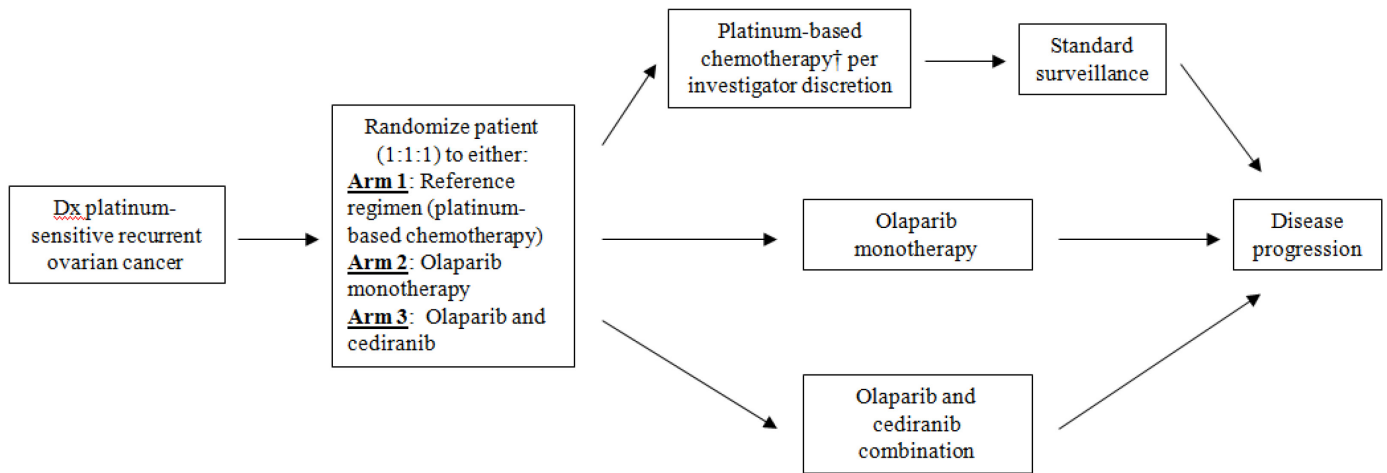
A Phase III study comparing single-agent olaparib or the combination of cediranib and olaparib to standard platinum-based chemotherapy in women with recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer

NCI Version Date: 08/15/2019

Lead Organization: NRG / NRG Oncology

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For regulatory requirements:	For patient enrollments:	For study data submission:
<p>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal:</p> <p>Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)</p> <p>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.</p> <p>Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</p>	<p>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYS_TEM/ or https://OPEN.ctsu.org.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</p>	<p>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</p>
<p>The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.</p>		
<p>For clinical questions (i.e. patient eligibility or treatment-related) <i>contact the Study PI of the Lead Protocol Organization</i></p>		
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SCHEMA



†Platinum-based chemotherapy options may include carboplatin and paclitaxel, carboplatin and gemcitabine, or carboplatin and pegylated liposomal doxorubicin (further detailed in Section 5.1). (11/07/2016)

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1.0 OBJECTIVES

1.1 Primary Objective

- 1.1.1 Assess the efficacy of either single agent olaparib or the combination of cediranib and olaparib, as measured by PFS, as compared to standard platinum-based chemotherapy in the setting of recurrent platinum-sensitive ovarian, primary peritoneal or fallopian tube cancer.

1.2 Secondary Objectives

- 1.2.1 Assess the efficacy of single agent olaparib or the combination of cediranib and olaparib, as measured by response rate, and overall survival as compared to standard platinum-based chemotherapy in the setting of recurrent platinum-sensitive ovarian, primary peritoneal or fallopian tube cancer.

1.3 Objectives with Integral Biomarkers

- 1.3.1 Assess the efficacy of single agent olaparib or the combination of cediranib and olaparib, as measured by PFS, in women with or without deleterious germline BRCA mutations (gBRCAmt) in the setting of recurrent platinum-sensitive ovarian, primary peritoneal, or fallopian tube cancer.

1.4 Objectives with Integrated Biomarkers

- 1.4.1 Assess the effect on disease-related symptoms (DRS) as measured by the 9-item DRS-P subscale of the NCCN-FACT Ovarian Symptom Index-18 (NFOSI-18), of single agent olaparib or cediranib and olaparib, compared to standard platinum-based chemotherapy, in the setting of recurrent platinum sensitive ovarian, primary peritoneal or fallopian tube cancer.
- 1.4.2 Assess the efficacy of single agent olaparib or the combination of cediranib and olaparib, as measured by PFS, in women with or without homologous repair deficiencies as measured by BROCA in the setting of recurrent platinum-sensitive ovarian, primary peritoneal, or fallopian tube cancer.
- 1.4.3 To assess changes in the number of circulating endothelial cells (CECs) following three days of treatment with olaparib, combination olaparib/cediranib, or standard platinum-based chemotherapy in women with recurrent platinum-sensitive ovarian, primary peritoneal, or fallopian tube cancer
- 1.4.4 To assess whether change in the number of circulating endothelial cells (CECs) following three days of treatment with olaparib, combination olaparib/cediranib, or standard platinum-based chemotherapy in women with recurrent platinum-sensitive ovarian, primary peritoneal, or fallopian tube cancer is prognostic for PFS.

- 1.4.5 To develop a profile from a panel of angiogenic biomarkers in women with recurrent platinum-sensitive ovarian, primary peritoneal, or fallopian tube cancer which is associated with PFS, and then validate the predictive value of this biomarker profile.

1.5 Exploratory Objectives

- 1.5.1 To assess the time from randomization to the first non-study, anti-cancer therapy, surgery or death (TFST) for single-agent olaparib or combination cediranib and olaparib relative to standard platinum-based chemotherapy in the setting of recurrent platinum-sensitive ovarian, primary peritoneal or fallopian tube cancer.
- 1.5.2 To assess the time from randomization to the second non-study, anti-cancer therapy, surgery or death (TSST) for single-agent olaparib or combination cediranib and olaparib relative to standard platinum-based chemotherapy in the setting of recurrent platinum-sensitive ovarian, primary peritoneal or fallopian tube cancer.
- 1.5.3 Assess the effect on secondary measures of quality of life, as assessed by the treatment side effects (TSE) and function / well-being (F/WB) subscales of the NFOSI-18, sensory neuropathy as measured by the FACT/GOG-Ntx-4, and health utility as measured by the EQ-5D, of single agent olaparib or cediranib and olaparib, compared to standard platinum-based chemotherapy, in the setting of recurrent platinum sensitive ovarian, primary peritoneal or fallopian tube cancer.

2.0 BACKGROUND

2.1 Platinum-sensitive ovarian cancer

Ovarian cancer remains the leading cause of death from gynecologic malignancy in the United States. For patients with platinum-sensitive recurrence (defined as disease recurring at least 6 months after the last receipt of platinum-based chemotherapy), additional platinum-based therapy has been the general standard-of-care. Regimens used in this setting include platinum-based doublets such as carboplatin and paclitaxel, carboplatin and gemcitabine, and carboplatin and pegylated liposomal doxorubicin (PLD) (Pfisterer, Ledermann, 2006).

Randomized clinical trials have demonstrated that the combination of carboplatin and paclitaxel and carboplatin and gemcitabine are effective therapies in this setting (Parmar, 2003), (Pfisterer, Plante, 2006). The combination of carboplatin and PLD has also been shown to be equivalent to that of carboplatin and paclitaxel in the setting of recurrent platinum-sensitive ovarian cancer (Pujade-Lauraine, 2010). Repeat platinum-based chemotherapies carry increased side effects, including risk of allergic reaction to platinum as well as worsening neuropathy or hematologic toxicities. However, few alternatives to platinum-based chemotherapy in the recurrent platinum-sensitive setting exist.

2.2 Activity of olaparib and other PARP-inhibitors (PARPi's) in ovarian cancer

PARPi's are an emerging class of drugs, and development of these agents in ovarian cancer is of significant interest (Liu, 2014). Olaparib is an oral PARPi that has demonstrated activity both in women with BRCA-related and BRCA-wild type ovarian cancer, with reported response rates of ~40% in BRCA mutation carriers and 24% of non-BRCA mutation carriers (Gelmon, 2011). Nonetheless, a Phase 2 study comparing olaparib monotherapy to PLD therapy in women with BRCA-related ovarian cancer recurring <12 months after last receipt of platinum-therapy found no advantage to olaparib therapy in this setting, with a median PFS observed with single-agent olaparib at 400mg BID in the capsule formulation of 8.8 months (Kaye, 2012).

Additionally, significant activity was demonstrated of olaparib maintenance therapy following completion of platinum-based chemotherapy in women with platinum-sensitive high-grade serous ovarian cancer (Ledermann, 2012). In this randomized Phase 2 study, women were randomized to receive either maintenance olaparib or placebo, and the median PFS was increased from 4.8 months to 8.4 months in the cohort as a whole. In a study subgroup including women with germline BRCA mutations (gBRCAmt) and those with somatic BRCA mutations, the median PFS increased from 4.3 months to 11.2 months (Ledermann, 2014).

As a single agent in ovarian cancer, olaparib and other PARP-inhibitors have demonstrated activity in platinum-sensitive patients, including those without a germline or somatic BRCA mutation. In a randomized phase 2 trial comparing single-agent olaparib to combination cediranib/olaparib, a median PFS of 9.0 months with olaparib monotherapy was observed, which falls within the range of activity typically observed with platinum-based chemotherapy. In a separate Phase 2 trial in women of the PARP-inhibitor rucaparib in women with platinum-sensitive recurrent ovarian cancer, a median PFS was reported of 9.4 months in women with germline or somatic BRCA mutation and of 7.1 months in women without a BRCA mutation but whose tumors demonstrated a signature suggesting the presence of HR deficiency (McNeish, 2015). Research has also demonstrated that the use of olaparib does not jeopardize response to future standard of care therapy, with women with heavily pre-treated (median 3 prior lines) ovarian cancer demonstrating an overall response rate of 36% to chemotherapy and 40% to platinum-based agents after having progressed on prior olaparib therapy (Ang, 2013).

2.3 Activity of cediranib in ovarian cancer

Cediranib is a small-molecule kinase inhibitor of VEGFR with demonstrated activity in both platinum-sensitive and platinum-resistant ovarian cancer (Matulonis, 2009). The overall response rate to single-agent cediranib in a Phase 2 trial was 17% in the overall population, with a response rate of 12.5% in platinum-sensitive patients and 20% in platinum-resistant patients; the median PFS was 5.2 months. A second Phase 2 trial preliminarily reported 4 PRs in 60

patients, with a median time to progression of 4.1 months in women with recurrent ovarian cancer (Hirte, 2008).

ICON6 recently demonstrated that the combination of cediranib together with platinum-based chemotherapy and followed by cediranib maintenance, could extend progression-free and, preliminarily, overall survival, in women with platinum-sensitive ovarian cancer compared to chemotherapy alone (Ledermann, 2013).

2.4 Combination of cediranib and olaparib

Preclinical studies have demonstrated that angiogenesis inhibitors combined with PARPi's can have supra-additive effects. *In vivo* anti-angiogenic activity has been observed with PARPi's and in PARP-1 knockout mice (Tentori 2007). Additionally, downregulation of homologous recombination repair genes, such as *BRCA1* and *RAD51*, has been observed in conditions of hypoxia, with enhancement of PARPi sensitivity in the hypoxic setting (Bindra, 2004; Bindra, 2005). Preclinical work has demonstrated that cediranib and olaparib have potential synergistic activity *in vitro* in decreasing tumor cell invasion and blood vessel growth (Figure 1).

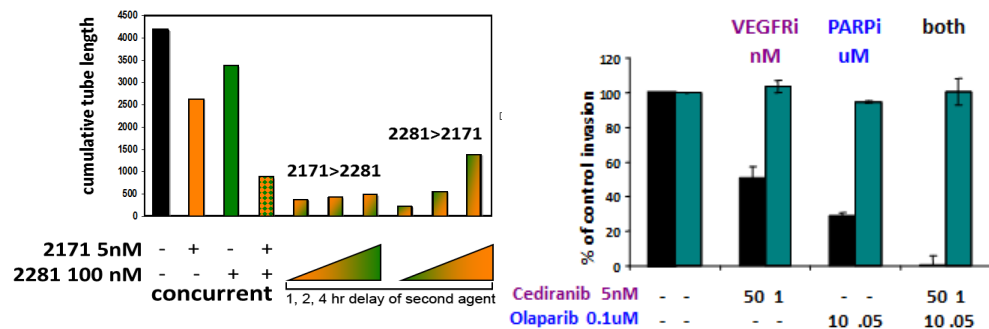


Fig 1: Cediranib and olaparib combine effectively to (A) reduce invasion and (B) reduce microvascular cell tube organization as compared to either agent alone.

Pre-clinical synergy exists between olaparib and cediranib in inhibiting both ovarian cancer cell invasion and microvascular endothelial cell tube formation *in vitro* (unpublished data). Promising preliminary activity against recurrent ovarian cancer was seen in our Phase 1 dose-finding trial of the combination of cediranib and olaparib, which yielded an objective response rate of 44% (Bouwman, 2010).

A Phase 1 trial was previously conducted to establish the recommended Phase 2 dosing (RP2D) of cediranib in combination with olaparib (capsule formulation), which

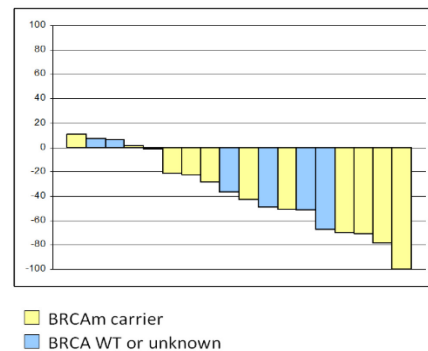


Fig 2: Best response in ovarian cancer patients of cediranib/olaparib in dose-escalation Phase 2 study.

enrolled a total of 28 patients (20 ovarian, 8 breast) (Liu, 2013). A response rate of 44% to the cediranib/olaparib combination was observed in this Phase 1 population, which included both BRCA mutation carrier and non-carrier patients. A waterfall plot of the observed activity is shown in Figure 2. The RP2D was found to be cediranib 30mg daily with olaparib capsule 200mg twice daily.

2.5 Phase 2 experience with cediranib and olaparib combination

A multi-center open-label randomized Phase 2 trial comparing the activity of the cediranib and olaparib combination to olaparib alone in platinum-sensitive recurrent ovarian cancer randomized 90 patients in a 1:1 ratio to either the combination or single-agent olaparib (capsule formulation) (Liu, 2014). Eligibility criteria for this trial included platinum-sensitive disease recurrence, with platinum-sensitivity defined as recurrence occurring greater than or equal to 6 months after the last platinum-containing regimen. Patients were allowed to receive an unlimited number of platinum-based lines of therapy, and up to one non-platinum-based regimen in the recurrent setting. No anti-angiogenics in the recurrent setting were allowed; no prior PARP-inhibitors were allowed.

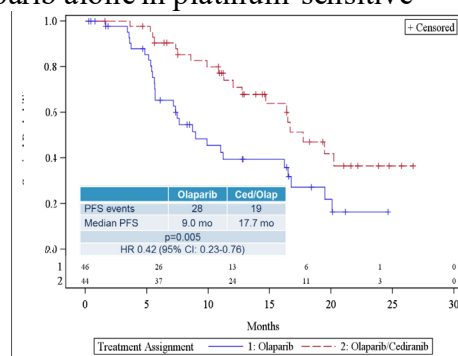


Fig 3: Kaplan-Meier PFS curves in patients treated on olaparib and cediranib/olaparib in Phase 2 trial.

The combination of cediranib and olaparib significantly extended both PFS and overall response rate (ORR) compared to olaparib alone in this patient population, with a median PFS of 9.0 months for olaparib alone and 17.7 months for cediranib/olaparib (HR 0.418, 95% CI 0.229-0.763, $p = 0.005$) (Figure 3). There were 2 complete responses (CR) and 20 partial responses (PR) in patients on olaparib alone (48% ORR) and 5 CRs and 30 PRs in patients on cediranib/olaparib (80% ORR, $p = 0.002$).

Forty-seven of the 90 patients enrolled to the Phase 2 cediranib/olaparib vs. olaparib trial were known BRCA mutation carriers (25 olaparib; 23 cediranib/olaparib). A post-hoc subset analysis of PFS by BRCA mutation status (carrier vs. non-carrier/unknown) is shown in Figure 4 (next page). In BRCA mutation carriers, the median PFS was 16.5 months on the olaparib alone arm and 19.4 months on the cediranib/olaparib arm (HR 0.55, 95% CI 0.24-1.27, $p = 0.16$). In BRCA non-carrier/unknown patients, the median PFS was 5.7 months on the olaparib alone arm, and 16.5 months in the cediranib/olaparib arm (HR 0.32, 95% CI 0.14-0.74, $p = 0.008$).

Differentially occurring grade 3 or 4 toxicities attributed to study treatment included fatigue (27% cediranib/olaparib vs 11% olaparib, $p = 0.06$), diarrhea (23% vs 0%, $p = 0.0004$), and hypertension (41% vs 0%, $p < 0.0001$). There were

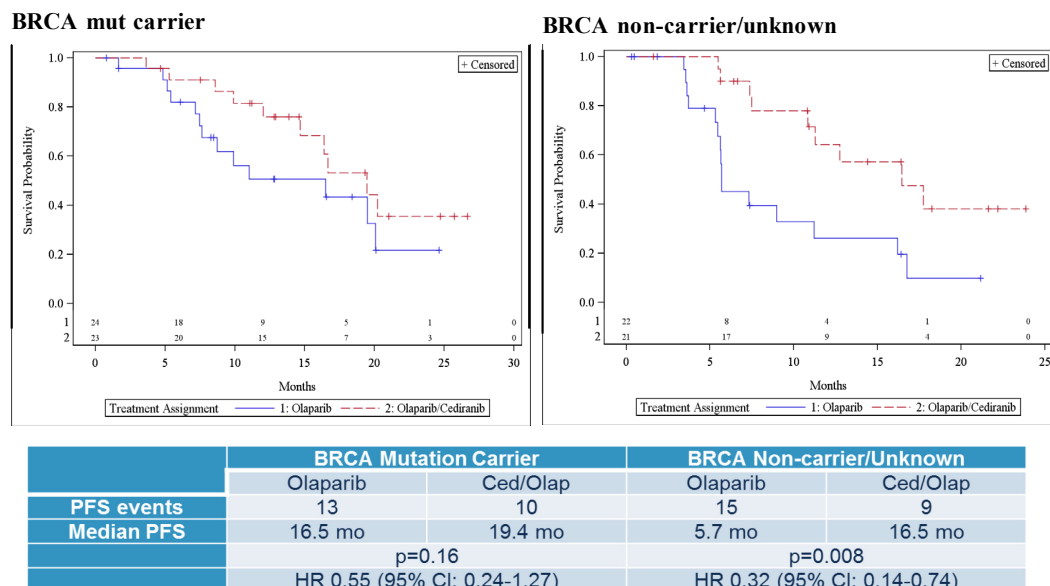


Fig 4: Kaplan-Meier PFS curves in gBRCAm and BRCA non-carrier/unknown patients.

two Grade 4 events, both in the cediranib/olaparib arm: 1 grade 4 hypertension in a patient who was not fully compliant with blood pressure monitoring and 1 grade

4 myelodysplastic syndrome (MDS). The patient with MDS had two prior lines of therapy and had been on study for approximately 1 year when she was diagnosed with MDS. Four patients on the cediranib/olaparib arm withdrew from study treatment secondary to toxicity (1 each due to weight loss, MDS, recurrent avascular necrosis in the setting of prior history of avascular necrosis, and vaginal fistula formation). Otherwise, AEs were manageable with a combination of symptom management and dose holds and/or reductions, and removal from the study for reasons other than a PFS event was balanced between the arms (2 withdrawal of consent, 1 investigator decision, 5 clinical progressions on cediranib/olaparib vs. 3 withdrawal of consent, 1 investigator decision, and 6 clinical progressions on olaparib alone).

Overall, the results of the Phase 2 trial comparing cediranib/olaparib to olaparib alone in platinum-sensitive recurrent ovarian cancer demonstrated that the combination results in increased activity, as measured both by PFS and ORR. Toxicities were consistent with expected class-related toxicities of these drugs. A list of the results of the Phase 2 trial and that of single-agent olaparib or cediranib trials is shown in Table 1 on the next page.

Trial	N	PFS (mo)	ORR (RECIST) (%)
<u>Olap / Ced rand Ph 2</u>			
Olap 400mg BID	46	9.0	56.1
Ced 30mg QD/olap 200mg BID	44	17.7	83.7
<u>Study 12 (Olap vs. PLD) rand Ph 2 (Kaye, JCO 2012)</u>			
Olap 200mg BID	32	6.5	25
Olap 400mg BID	32	8.8	31
PLD 50mg/m2	33	7.1	18
<u>Olap single-arm Ph2 (Gelmon, Lancet Oncol 2011)</u>			
All ovarian (N = 63 RECIST-eval)	63	7.3	29
BRCAm	17	7.4	41 (3/5 plat-s)
BRCA-WT	46	6.4	24 (10/20 plat-s)
<u>Ced single-arm Ph2 (Matulonis, JCO 2009)</u>			
Overall	47 (ITT)	5.2	17
Platinum-sensitive	16	5.2	12.5 (6 pts off early for tox)
Platinum-resistant	30	5.2	17 (5 pts off early for tox)
<u>Ced single-arm Ph2 (Hirte – abstract ASCO 2008)</u>			
Overall	60	4.1 (TTP)	
Platinum-sensitive	26	(no sig diff	3 PRs (of 17 pts)
Platinum-resistant	34	between groups)	1 PR (of 24 pts)

2.6 Rationale for trial design

Repeat platinum-based chemotherapies carry increased side effects, including risk of allergic reaction to platinum as well as worsening neuropathy or hematologic toxicities. However, few alternatives to platinum-based chemotherapy in the recurrent platinum-sensitive setting exist. The PFS point estimate of 17.7 months on the cediranib/olaparib arm of the Phase 2 trial compares favorably with the median PFS range of between 8.4 months to 13 months (Parmar, 2003), (Pfisterer, Plante, 2006), (Pujade-Lauraine, 2010), (Ledermann, 2013), (Aghajanian, 2012) reported in studies of platinum-based doublets in platinum-sensitive ovarian cancer, and the observed PFS of 9.0 months on the olaparib monotherapy arm also falls within the range observed with platinum-based chemotherapy. These results suggest that these biologic therapies may present an alternative to standard platinum-based chemotherapy in these women with an incurable recurrent ovarian cancer, and we therefore propose to compare the efficacy of single-agent olaparib or the combination of cediranib/olaparib to that of standard platinum-based chemotherapy in this population.

This trial proposes to assess the efficacy and tolerability of single-agent olaparib versus the combination of cediranib and olaparib versus platinum-based chemotherapy in women with platinum-sensitive ovarian cancer. There is clinical equipoise for inclusion of a single-agent olaparib arm given the point estimates for median PFS for single-agent PARPi in Phase 2 trials have been within the range that have been reported for platinum-based chemotherapy. Additionally, research has suggested patients who have progressed on olaparib therapy continue to demonstrate response to standard of care chemotherapy, suggesting that the sequence of drug exposure dose not jeopardize clinical outcomes.

The trial design is a randomized Phase 3 trial that will randomize women with recurrent platinum-sensitive ovarian cancer in a 1:1:1 fashion to receive either olaparib, cediranib and olaparib, or platinum-based chemotherapy. The trial is powered to allow comparison of both experimental arms to the reference platinum-based chemotherapy arm for assessment of the primary endpoint, progression-free survival. This study will not be blinded or placebo controlled as the treatment regimens used vary by route of administration, schedules and anticipated drug related toxicities that make blinding less feasible and unnecessary. Interim futility analyses are included such that accrual of either the olaparib monotherapy or cediranib/olaparib combination arm could be halted if deemed futile.

2.7 Quality of Life

The effect on quality of life of olaparib alone or combination cediranib/olaparib, compared to standard platinum-based chemotherapy, will also be of high interest. In the absence of an overall survival (OS) benefit, it is challenging to place a value upon PFS. On the one hand, delaying cancer progression is likely to confer some benefit to a person's quality of life, not only because of the psychological benefit of knowing one's disease is stable, but also based upon the fact that delaying progression is also likely to delay the onset of life-limiting symptoms. On the other hand, treatment itself carries toxicities which themselves can be distressing and life-limiting. In order to fully appreciate the benefits and risks associated with delaying PFS, careful assessment of targeted quality of life domains, in particular, disease symptoms, but also treatment side effects, acceptability of therapy, and patient functioning, is required.

The patient reported outcome (PRO) plan for this trial was assembled to capture disease symptoms, treatment side effects, and general function and well-being. Disease related symptom benefit is the primary and only *planned* PRO analysis. Secondary (post hoc) evaluation of differences in side effects and function are also proposed, in order to estimate the extent to which symptoms and side effects affect function and well-being, and to plan for future study of the relative weight patients place upon each of these endpoints alongside clinical endpoints such as progression-free survival. We propose the following highly efficient measures:

- Disease-related symptoms: The NCCN/FACT-Ovarian Cancer Symptom Index-18 (NFOSI-18; Jensen et al, 2011). Half (9 items) of the NFOSI-18 comprise the Disease-Related Symptom-Physical (DRS-P) scale, which is the primary planned PRO endpoint
- Treatment side effects: We will employ two measures of treatment side effects: The 5-item Treatment Side Effects (TSE) scale from the NFOSI-18; and the 4-item FACT/GOG-Ntx-4 measure of sensory neuropathy)
- Patient function and well-being: We will employ three brief measures of patient function and well-being: The 3-item function and well-being (F/WB) scale from the NFOSI-18, the 1-item worry item from the NFOSI-18, the 5-item EQ-5D measure of patient preference (utility).

The patient reported outcome (PRO) plan for this trial was assembled to capture both disease symptoms and treatment side effects, placing disease symptom benefit as the primary outcome, with secondary evaluation of differences in side effects. In order to estimate the extent to which symptoms and side effects affect function and well-being, and to plan for future study of the relative weight patients place upon each of these alongside clinical endpoints such as progression-free survival, and in the context of treatment costs, we propose highly efficient measures of function/well-being (NFOSI-18 F/WB) and utility (EQ-5D).

Patient preferences for outcomes of treatment

Outcomes of the treatment of cancer that are important to clinicians and researchers are not always the same as those that are important to patients. We propose to evaluate patients' preferences for the attributes of their treatments, including not only overall survival and progression-free survival, but also the symptoms of cancer, side effects of treatments, and health utility. This will provide data elements that enable a more accurate and clinically relevant depiction of trial results for subsequent patients who have to face this challenging decision. (Note that the patient preference elicitation study will be done after the trial is completed, in a new cohort of women with advanced ovarian cancer, using clinical and patient-reported outcome data from this trial to inform the preference elicitation exercises. As such, we propose to collect sufficient information to inform this subsequent research in this trial).

The regimens being evaluated in this trial differ significantly on many levels. Cytotoxic chemotherapy regimens are typically administered for a shorter time period than biologics, have a different toxicity profile, and do not include ongoing maintenance treatment once a CR is achieved. Out of pocket cost for cytotoxics may be lower due to a more limited treatment period, and the fact that longstanding therapies typically carry lower costs. The data collected in these trials, including PRO and cost estimates, will be extremely useful for subsequent research that can formally elicit patient preferences for one or another treatment based on their personal perspectives on each of the outcomes measured in this trial (PFS, OS, symptoms, side effects, function/well-being, utility). One standard preference elicitation method is conjoint analysis, in which participants evaluate a series of treatment choices with a set of attributes of varying levels. This ultimately allows the assignment of preference weights that could be considered for development of a composite endpoint or development of a patient focused decision tool. Although conjoint analysis is not part of this protocol per se, the data obtained will inform such important work in the future, much the same as is now being done by these same investigators in the area of intraperitoneal versus intravenous chemotherapy. We emphasize that this important work can be done with only a very modest time commitment from patients of 10 minutes per assessment over a 3-year period, and minimal cost to the trial.

With the exception of the DRS-P, the rationale and analysis plan for these PRO endpoints can be found in Appendix X. Our proposed PRO assessment comprises

a total of 27 questions to measure symptoms, side effects, function, and well-being. This is a shorter assessment than has been used in prior GOG trials that have consistently seen >80% follow-up assessment adherence. Patient time to complete averages less than 10 minutes for the entire set of questions, and this has historically been a very motivated and engaged group of participants. To keep the assessment brief, questions were selected only if they served a specific and planned purpose as described below and in Appendix X.

Study Hypotheses and Instrument Selection

The overarching hypothesis is that the treatment arm associated with a PFS benefit will also demonstrate a PRO benefit relative to the other(s). This is based on the underlying hypothesis that the disease symptom benefit of delaying progression will be greater than any differences in toxicities that might exist between treatments. In order to test this hypothesis properly, it is critically important that all living patients be assessed even after progression, for the full follow-up window specified in the protocols. If, as has been the case in many prior trials, PRO assessment stops at the time of progression, this will introduce a bias in the group comparison, one which typically disadvantages the more effective treatment (because it retains more patients, including some who may share similarity with patients who have progressed on the inferior treatment).

In the PRO component of this trial, a primary emphasis will be placed on symptoms of disease (with the understanding that some symptoms such as fatigue and nausea are caused by both disease and treatment), and secondary emphasis on treatment side effects and burden/acceptability of treatment. The tolerability of small molecule inhibitors as compared to standard chemotherapy will also be of high interest in this population. Therefore, additional important questions that will be addressed by this trial include the assessment of disease related symptoms as an important secondary endpoint to evaluate the benefit of PFS as experienced by the patient, including the question of whether symptomatic progression accompanies radiographic progression. Similarly, the patient experience of side effects (at least the more common or consequential ones) will be an important indicator of the acceptability of one treatment relative to another and will therefore also be assessed.

Our proposed PRO assessment comprises a total of 27 questions to measure symptoms, side effects, function, and well-being. This is a shorter assessment than has been used in prior GOG trials that have consistently seen >80% follow-up assessment adherence. Patient time to complete averages less than 10 minutes for the entire set of questions, and this has historically been a very motivated and engaged group of participants. To keep the assessment brief, questions were selected only if they served a specific and planned purpose as described below.

The Disease-Related Symptom-Physical (DRS-P) scale from the NCCN/FACT-Ovarian Cancer Symptom Index-18 (NFOSI-18), (Jensen, 2011), is a 9-item scale which comprises the first 9 items of the NFOSI-18. This scale was developed

using a qualitative methodology with 50 advanced ovarian cancer patients and 10 expert clinicians. Most of the items come from the FACT-O questionnaire (Basen-Engquist, 2001), but they have been supplemented, reorganized and validated to create a set of targeted outcome tools for disease related symptoms, treatment side effects, and general functioning and well-being. Of note, after establishing that these 9 questions are the most important disease-related symptoms to women with ovarian cancer (Jensen, 2011), these questions have been further evaluated and demonstrated through cognitive debriefing interviews with 18 women with ovarian cancer to be understood as intended. The targeted 9-item DRS-P subscale will serve as the main PRO endpoint. Treatment side effects, as summarized by a five-item subscale also included within the NFOSI-18, is a secondary PRO endpoint.

The hypothesis, as stated above, is that the treatment arm with the superior PFS benefit will also have a superior DRS-P benefit, lending confirmation as a patient-reported symptomatic benefit associated with delaying disease progression.

2.8 Translational Science Background

2.8.1 Homologous Recombination Defect (HRD) Studies

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 (HR)-mediated DNA repair. Other genes in this pathway (*BRIPI/FANCI*, *PALB2/FANCD1*, *RAD51C/FANCD2*, *RAD51D*) also contribute to hereditary breast and ovarian cancer (Walsh, 2011; Pennington, 2012; Loveday, 2011; Rafnar, 2011; Meindl, 2010). The Cancer Genome Atlas Network (TCGA) recently suggested that up to half of serous ovarian carcinomas have HR defects (HRD), but that estimate was based on a variety of molecular findings, many with uncertain impact on DNA repair function (Cancer Genome Atlas Research Network, 2011). PARPi's demonstrate synthetic lethality in cells with HRD, including cells deficient in *BRCA1/2* (Bryant, 2005; Farmer, 2005). 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 (Audeh, 2010; Kaye, 2012). Importantly, approximately 25% of serous ovarian cancers that are wildtype for *BRCA1/2* also respond to PARPi (Gelmon, 2011).

Germline *BRCA1/2* mutations (gBRCAm) are the prototype molecular alterations that confer HRD (Bryant, 2005; Farmer, 2005). *BRCA1* and *BRCA2* somatic mutation (sBRCAm) occur in approximately 6% of cases (Cancer Genome Atlas Research Network, 2011; Pennington, 2014), and also appear to confer sensitivity to PARP inhibitors (Ledermann, 2014). PARP inhibitors also selectively kill cells in vitro that are deficient in other homologous recombination genes including *RAD51D*, *NBN*, *ATM*,

and *CHEK2* (Loveday, 2011; McCabe, 2006). 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 survival¹³. 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 (Pennington, 2014).

BRCA1 promoter methylation down regulates BRCA1 message and protein expression and occurs in 10-15% of ovarian carcinomas (Baldwin, 2000; Esteller, 2000). Unlike *BRCA1* mutations, *BRCA1* methylation does not correlate with platinum response to therapy or overall survival (Cancer Genome Atlas Research Network, 2011; Swisher, 2009). Therefore, the role of *BRCA1* methylation in PARPi response is uncertain. In contrast, BRCA1 protein reduction occurs in 30-40% of ovarian carcinomas and is associated with better overall survival after platinum chemotherapy (Swisher, 2009; Thrall, 2006). The role of *BRCA1* promoter methylation and protein expression will be evaluated as exploratory biomarkers for response and correlation with treatment efficacy in this study.

In order to respond to a PARP inhibitor, cancer cells need to be deficient in homologous recombination but also proficient in the alternative error prone non-homologous end joining (NHEJ) DNA repair pathway (Patel, 2011; Adamo, 2010). 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 priori 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 (Nik-Zainal et al., 2012; Wang et al., 2012; Birkbak et al., 2012). 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.

2.8.2 BROCA-HR

The marked susceptibility of patients with gBRCAm-associated cancers has validated gBRCAm as a predictive biomarker for PARP inhibitor (PARPi) response (Fong, 2009). Other mechanisms of HRD may be a functional biomarker for response to DNA damaging agents and PARPi. Thus, it is important to identify which ovarian cancer patients have germline or somatic mutations in HRD genes and to examine their potential as predictive biomarkers.

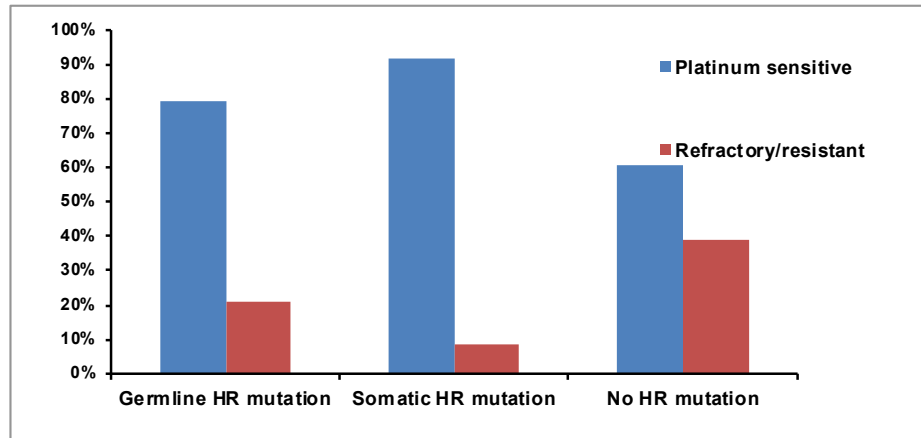


Figure 5. Presence of HR mutation is predictive of improved primary response to platinum.

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 (Walsh, 2011). 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 (FANCF)*, *RAD51D*, *RAD51C (FANCO)*, and *PALB2 (FANCL)* (Walsh, 2011; Wickramanayake, 2012). 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) (Pennington, 2014). The

presence of either a germline or somatic FA/HR mutation is highly predictive of an improved primary response to platinum chemotherapy ($P < .0005$, Figure 5) and longer overall survival ($P = .001$, Figure 6; Pennington, 2014). Germline and somatic loss of function mutations were identified in all of the 13 FA/HR genes evaluated.

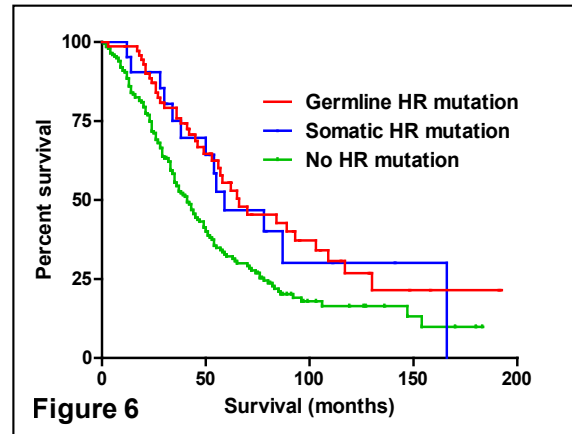


Figure 6

Given the observed association between response to PARPi and platinum-sensitivity (Fong, 2010), we hypothesize that the BROCA-HR test will identify subsets of ovarian cancer patients with HRD with increased sensitivity to olaparib or cediranib/olaparib combination, and may yield biomarkers with potential to guide administration of these therapies.

2.8.3 Circulating Endothelial Cells (CEC) (11/07/2016)

The presence of circulating endothelial cells (CEC) has been recognized as a potential biomarker of vascular damage (Bertolini, 2006). Elevated numbers of CEC have been described in lymphoma, melanoma, and other solid tumors including ovarian cancer, reflecting the perturbation of vascular endothelium (Goon, 2006). A related circulating cell population is endothelial progenitor cells (CEP), which originate from the bone marrow, rather than from vessel walls and related to tumor angiogenesis (Rafii, 2002). We recently reported prospectively planned exploratory biomarker endpoints in the phase II study of the combination of olaparib and cediranib (Lee et al., ASCO 2014, manuscript in preparation). We hypothesized assessment of vascular endpoints within the olaparib/cediranib study would identify lead biomarker candidates. A subset of eligible patients voluntarily participated in the translational study at NCI. Blood samples were collected pre- and day 3 of therapy to measure circulating endothelial cells (CEC: nucleated CD133-CD146+CD31+CD45-), circulating endothelial progenitor cells (CEP: viable nucleated CD133+, CD146-, CD31+ CD45 - or dim) in 12 patients. Patients receiving both agents had a median 3.5 fold increase in CEC compared to 0.7 for olaparib patients alone ($p=0.032$, Figure 6). CEC fold increase pretreatment to day 3 correlated with survival ($r=0.88$, 95%CI 0.55-0.97, $p<0.001$; Figure 7).

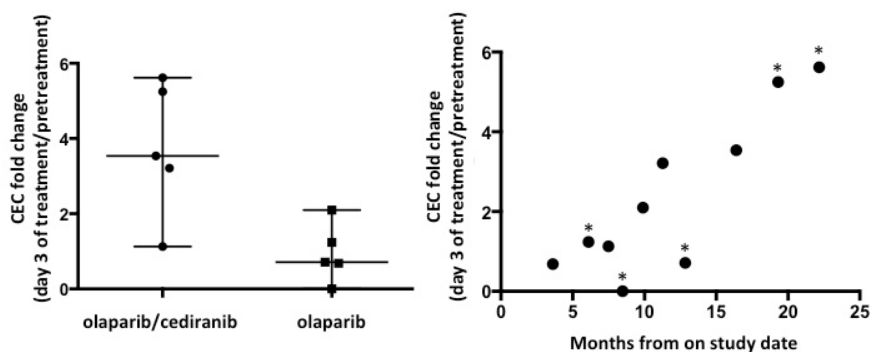


Figure 7. A. Patients receiving olaparib/cediranib had a larger fold increase median increase in CEC compared to olaparib alone ($p=0.032$). B. The fold increase in CEC on day 3 was associated with survival in all patients ($r=0.88$, 95%CI 0.55-0.97, $p<0.001$). *Times at risk were censored on the date of their last contact for those women who were last reported a live and progression-free.

Vascular injury is known to be accompanied by an induction in CEC production (Lin, 2013). CEC/CEP have been examined in early clinical trials using anti-angiogenics (Ning, 2010; Park, 2013; Kummar, 2011). In the phase 2 study of docetaxel/prednisone v. docetaxel/prednisone with bevacizumab and thalidomide in metastatic prostate cancer, the numbers of post-treatment CEC inversely correlated with PSA response to the combinations of bevacizumab/thalidomide/docetaxel/prednisone (Ning,

2010); patients with $\geq 75\%$ PSA decline had an increase in CEC levels compared with those who had $< 75\%$ PSA decline ($p=0.02$).

Our exploratory translational studies demonstrate that olaparib/cediranib caused vascular injury indicated by increase of CEC. These findings support the hypothesis that cediranib and olaparib combination may yield greater inhibition in tumor vascularity and these changes may correlate with response rate and result in survival benefit.

2.8.4 Plasma Angiome

To date, the effort to identify candidate predictive blood-based markers for anti-angiogenic inhibitors has been challenging for many reasons. These include biological complexity, limitations of available reagents, limited sample collection in most trials, and a lack of randomization, which is needed to deal with the potential confounding of prognostic and predictive markers. Many of these barriers have now been overcome. Compared to tissue-based biomarkers, blood-based biomarkers have the significant advantages of low cost, universal applicability, and the ability to be followed over the course of a patient's treatment. By focusing on soluble factors of known biological relevance, further scientific, diagnostic, and therapeutic efforts are greatly facilitated.

The application of multiplex ELISA approaches in clinical samples is rapidly evolving, having only recently shown positive results. The design of the Duke multiplex panel array to interrogate diverse biologies related to angiogenesis is novel. Many of the analytes in our multiplex array were developed and optimized for performance in plasma and serum samples from cancer patients. The Duke plasma angiome approach utilizes the Searchlight™ platform from Aushon BioSystems Inc, and the panel has been developed in tandem with the team at Aushon for over 7 years to develop multiple new assays and optimize the performance of our specific panel design (see Table 3).

Table 3: Plasma-based marker identification

Soluble Angiogenic Factors		Matrix-Derived Factors	Markers of Vascular Activation and Inflammation
ANG-2	PDGF-BB	sEndoglin	CRP
bFGF	PIGF	Osteopontin	ICAM-1
HGF	VEGF-A	TGFβ1	IL-6
IGFBP1	VEGF-D	TGFβ2	PAI-1 Active
IGFBP2	sVEGFR1	TGFβRIII	PAI-1 Total
IGFBP3	sVEGFR2	TIMP1	SDF-1
PDGF-AA	sVEGFR3	TSP2	VCAM-1

This approach is technically robust and readily adaptable to clinical practice. Because this data will be derived from patients, even preliminary data may significantly improve our understanding of how angiogenesis and tumor growth factors are regulated in cancer patients. Promising findings can be followed up in future clinical studies and in preclinical models. Because the Duke Angiome lab serves as the core lab for multiplex ELISA analyses within the Alliance, the current ovarian cancer profiling can be compared to the profiles seen in other phase III studies, helping to optimize future profiling approaches and provide the disease specific context needed for clinically meaningful companion diagnostics. Given the results of this prior work and the work of others, we anticipate being able to identify and validate or refute candidate markers of benefit that are specific for anti-angiogenic agents.

2.9 Inclusion of Women and Minorities

NRG and NRG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire population treated by participating institutions.

3.0 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the NRG Statistical and Data Management Center-Buffalo Office (via the contact list on the NRG web site).

3.1 Eligibility Criteria (11/07/2016) (07/31/2017)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

- 3.1.1 Patients must have platinum-sensitive recurrent high-grade serous or high-grade endometrioid ovarian, primary peritoneal, or fallopian tube cancers.

Patients with other (clear cell, mixed epithelial, undifferentiated carcinoma, or transitional cell carcinoma) high-grade histologies are also eligible, provided that the patient has a known deleterious germline BRCA1 or BRCA2 mutation identified through testing at a clinical laboratory.

Note: Due to the long acceptance of germline BRCA testing through Myriad, Myriad testing will be accepted. If testing for germline BRCA is done by other organizations, documentation from a qualified medical professional (e.g., ovarian cancer specialty physician involved in the field, high risk genetics physician, genetics counselor) listing the mutation and confirming that the laboratory results showed a recognized germline

deleterious BRCA1 or BRCA2 mutation or BRCA rearrangement is required. Please collect a copy of Myriad or other BRCA mutational analysis (positive or VUS or negative) reports.

3.1.1.1 Platinum-sensitive disease defined as no clinical or radiographic evidence of disease recurrence for > 6 months (or 182 days) after last receipt of platinum-based therapy.

3.1.1.2 Patients must have had a complete clinical response to their prior line of platinum therapy and cannot have had progression through prior platinum-based therapy.

3.1.2 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.1.3 Patients must have evaluable disease – defined as one of the following:

3.1.3.1 RECIST 1.1 measurable disease OR

3.1.3.2 Evaluable disease (defined as solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 definitions for target lesions OR ascites and/or pleural effusion that has been pathologically demonstrated to be disease-related)
AND a CA125 that has doubled from the post-treatment nadir and is also greater than 2 times ULN.

3.1.4 Prior therapy:

3.1.4.1 Prior chemotherapy must have included a first-line platinum-based regimen with or without intravenous consolidation chemotherapy.

3.1.4.2 Patients may have received an unlimited number of platinum-based therapies in the recurrent setting.

3.1.4.3 Patients may have received up to 1 non-platinum-based line of therapy in the recurrent setting. Prior hormonal therapy will not be considered to count as this non-platinum-based line.

3.1.4.4 Patients may not have had a prior anti-angiogenic agent in the recurrent setting. Prior use of bevacizumab in the upfront or upfront maintenance setting is allowed.

3.1.4.5 Patients may not have previously received a PARP-inhibitor.

3.1.4.6 Prior hormonal-based therapy for ovarian, primary peritoneal, or fallopian tube cancer is acceptable.

- 3.1.5 Patients must have an ECOG Performance Status of 0, 1 or 2 (Karnofsky \geq 60% (See Appendix I)
- 3.1.6 Patients must have adequate organ and marrow function, including:
 - 3.1.6.1 Absolute neutrophil count \geq 1,500/mcL
 - 3.1.6.2 Platelets \geq 100,000/mcL
 - 3.1.6.3 Hemoglobin \geq 10 g/dL
 - 3.1.6.4 Creatinine \leq the institutional upper limit of normal (ULN) OR creatinine clearance \geq 60 mL/min/1.73 m² for patients with creatinine levels above institutional normal.
 - 3.1.6.5 Urine protein: creatinine ratio (UPC) of \leq 1 or less than or equal to 2+ proteinuria on two consecutive dipsticks taken no less than 1 week apart. UPC is the preferred test. Patients with \geq 2+ proteinuria on dipstick must also have a 24 hour urine collection demonstrating \leq 500mg over 24 hours.
 - 3.1.6.6 Total bilirubin \leq 1.5x the institutional ULN
 - 3.1.6.7 AST (SGOT) and ALT (SGPT) \leq 3 times institutional ULN.
- 3.1.7 Toxicities of prior therapy (excepting alopecia) should be resolved to less than or equal to Grade 1 as per NCI-CTCAE (located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Patients with long-standing stable grade 2 neuropathy may be considered after discussion with the overall PI, but may not receive carboplatin and paclitaxel as the reference regimen, if randomized to that arm.
- 3.1.8 Patients must be able to swallow and retain oral medications and without gastrointestinal illnesses that would preclude absorption of cediranib or olaparib.
- 3.1.9 Patients must have adequately controlled blood pressure (BP), with a BP no greater than 140 mmHg (systolic) and 90 mmHg (diastolic) for eligibility. Patients must have a BP of \leq 140/90 mmHg 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 three antihypertensive medications. It is strongly recommended that

patients who are on three antihypertensive medications be followed by a cardiologist or blood pressure specialist for management of blood pressure while on protocol.

3.1.10 Patients must be willing and able to check and record daily blood pressure readings. Blood pressure cuffs will be provided to patients randomized to Arm III. Please refer to sections 9.7, and Appendix IX.

3.1.11 Cediranib has been shown to terminate fetal development in the rat, as expected for a process dependent on VEGF signaling. For this reason, women of child-bearing potential must have a negative pregnancy test prior to study entry. Women of child-bearing potential must agree to use two reliable forms of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 weeks after cediranib discontinuation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.12 Adequately controlled thyroid function, with no symptoms of thyroid dysfunction and TSH within normal limits.

3.1.13 Age \geq 18.

3.2 Ineligibility Criteria (11/07/2016)

Patients with one or more of the following conditions are NOT eligible for this study.

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) of starting treatment or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. Patients may not have had hormonal therapy within 2 weeks prior to entering the study. Patients receiving raloxifene for bone health as per FDA indication may remain on raloxifene absent other drug interactions.

3.2.2 Patients may not be receiving any other investigational agents nor have participated in an investigational trial within the past 4 weeks.

3.2.3 Patients may not be receiving any medication that may markedly affect renal function (*e.g.*, vancomycin, amphotericin, pentamidine).

3.2.4 Patients may not have received prior treatment affecting the VEGF pathway (including, but not limited to thalidomide, sunitinib, pazopanib, sorafenib, and nintedanib). Bevacizumab used in the upfront setting in

conjunction with chemotherapy and/or as maintenance to treat newly diagnosed disease will be allowed.

- 3.2.5 Patients may not have previously received a PARP inhibitor.
- 3.2.6 CA-125 only disease without RECIST 1.1 measurable or otherwise evaluable disease as per section 3.1.3.
- 3.2.7 Patients with untreated brain metastases, spinal cord compression, or evidence of symptomatic brain metastases or leptomeningeal disease as noted on CT or MRI scans should not be included on this study, since neurologic dysfunction may confound the evaluation of neurologic and other adverse events. Screening imaging to rule out brain metastases is not required for screening, but should be performed prior to study enrollment if clinically indicated. Patients with treated brain metastases and resolution of any associated symptoms must demonstrate stable post-therapeutic imaging for at least 6 months following therapy prior to starting study drug.
- 3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cediranib or olaparib.
- 3.2.9 Participants receiving any medications or substances that are strong inhibitors or inducers of CYP3A4 are ineligible. Refer to a frequently updated drug information reference for a list of strong inducers and inhibitors. See Appendix II.

Strong inhibitors and inducers of UGT/PgP should be used with caution.
- 3.2.10 History of gastrointestinal perforation. Patients with a history of abdominal fistula will be considered eligible if the fistula was surgically repaired or has healed, there has been no evidence of fistula for at least 6 months, and patient is deemed to be at low risk of recurrent fistula.
- 3.2.11 History of intra-abdominal abscess within the past 3 months.
- 3.2.12 Current signs and/or symptoms of bowel obstruction or signs and/or symptoms of bowel obstruction within 3 months prior to starting study drugs.
- 3.2.13 Dependency on IV hydration or TPN.
- 3.2.14 Any concomitant or prior invasive malignancies with the following curatively treated exceptions:

- 3.2.14.1 Treated limited stage basal cell or squamous cell carcinoma of the skin.
- 3.2.14.2 Carcinoma in situ of the breast or cervix.
- 3.2.14.3 Primary endometrial cancer meeting the following conditions:
Stage not greater than IA, grade 1 or 2, no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous/serous, clear cell, or other FIGO grade 3 lesions.
- 3.2.14.4 Prior cancer treated with a curative intent with no evidence of recurrent disease 3 years following diagnosis and judged by the investigator to be at low risk of recurrence.
- 3.2.15 Patients with any of the following:
 - 3.2.15.1 History of myocardial infarction within six months
 - 3.2.15.2 Unstable angina
 - 3.2.15.3 Resting ECG with clinically significant abnormal findings.
 - 3.2.15.4 NYHA classification of III or IV
- 3.2.16 If cardiac function assessment is clinically indicated or performed: LVEF less than normal per institutional guidelines, or <55%, if threshold for normal not otherwise specified by institutional guidelines.

Patients with the following risk factors should have a baseline cardiac function assessment:

 - 3.2.16.1 Prior treatment with anthracyclines
 - 3.2.16.2 Prior treatment with trastuzumab
 - 3.2.16.3 Prior central thoracic radiation therapy (RT), including RT to the heart
 - 3.2.16.4 History of myocardial infarction within 6 to 12 months (Patients with history of myocardial infarction within 6 months are excluded from the study)
 - 3.2.16.5 Prior history of impaired cardiac function
- 3.2.17 History of stroke or transient ischemic attack within six months.

- 3.2.18 Any prior history of hypertensive crisis or hypertensive encephalopathy.
- 3.2.19 Clinically significant peripheral vascular disease or vascular disease (including aortic aneurysm or aortic dissection).
- 3.2.20 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to starting cediranib.
- 3.2.21 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia (other than atrial fibrillation with controlled ventricular rate), or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.22 Pregnant women are excluded from this study because cediranib and olaparib are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with cediranib and olaparib, breastfeeding should be discontinued if the mother is treated with cediranib or olaparib. These potential risks may also apply to other agents used in this study.
- 3.2.23 Known HIV-positive individuals are ineligible because of the potential for pharmacokinetic interactions with cediranib or olaparib. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy.
- 3.2.24 Patients may not use any complementary or alternative medicines including natural herbal products or folk remedies as they may interfere with the effectiveness of the study treatments.
- 3.2.25 No features suggestive of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) on peripheral blood smear or bone marrow biopsy, if clinically indicated.
- 3.2.26 No prior allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUBCT).

4.0 REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

4.1 Pre-treatment assessments (11/07/2016) (07/31/2017)

The following observations and tests are to be performed and recorded on the appropriate form(s). Please note: Each entry refers to the corresponding footnote at the end of the table. Cycle 1 Day 1 should begin within 14 days of registration.

Assessments	Prior to Registration	Prior to Cycle 1 Day 1 Treatment
Informed Consent	A	
Medical History	A	
Physical Examination	A	C
Concomitant Medications	B	D
Performance Status	A	C
Toxicity Assessment	B	C
Vital Signs (Blood Pressure, Heart Rate, Temperature, and Pulse Oxygen Saturation)	A	D
Height and Weight	A	C
CBC/Differential/Platelets	B	C
Serum chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, total protein	B	C
TSH	B	C ^J
CA-125	B	C
Urine protein: creatinine ratio (preferred) or urinalysis	B	C
Electrocardiogram	B	C
MUGA or echocardiogram ^G	A ^G	
Pregnancy Test (if childbearing potential exists)	A	E ^F
Radiographic Tumor Measurement ^H	A	
Patient-reported outcome assessments		C
BRCA1/2 testing	I	

A: ≤ 28 days

B: ≤ 14 days

C: ≤ 7 days

D: Day of treatment

E: ≤ 3 days

F: The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of hCG.

G: MUGA or echocardiogram should be performed at baseline for all patients at increased risk for compromised LVEF, including patients with prior treatment with anthracyclines, prior treatment with trastuzumab, prior central thoracic RT, or history of myocardial infarction within the 12 months prior.

H: Radiographic tumor measurements should be obtained via imaging of at least the chest, abdomen, and pelvis at baseline. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline and subsequent assessments. Contrast CT is the preferred modality.

I: Comprehensive BRCA1/2 testing (at minimum, full sequencing of BRCA1 and BRCA2 in a CLIA-certified setting) must be available prior to randomization. Patients with prior BRCA1/2 testing should provide a formal copy of BRCA1/2 testing results, consisting of both the official BRCA1/2 testing report and, if appropriate, per 3.1.1, documentation by an appropriate qualified medical professional. Patients without prior testing or with less than comprehensive BRCA1/2 testing (as defined above), or those for whom testing results are not available, should have blood collected at screening for BRCA testing by the Comprehensive BRCA^{Analysis} (Myriad Genetics, Salt Lake City, UT, USA). BRCA1/2 testing kits for patients enrolling on GY004 may be obtained by contacting Alison Sibley (asibley@myriad.com) and Stephanie Hamilton (shamilto@myriad.com). The test requisition form and blood collection tube should be labeled with NCI site code, two patient initials, and patient DOB in the format *mmdyyy*. Do not include any spaces, dashes, etc. (e.g., NY123JD04051967). All information should be legibly written. If additional space is needed on the tube label, a separate label should be added. Any labeling discrepancies between the form and tube may cause delays in processing. All patients are required to be informed of the BRCA test results per their treating institution's practice. Patients may not be randomized until this genetic testing is completed and the results are available. All patients should be appropriately counseled regarding genetic risk and testing.

J: For participants in Arm III only.

4.2 Assessments during treatment (11/07/2016)

The following observations and tests are to be performed and recorded on the appropriate form(s). Please note: Each entry refers to the corresponding footnote at the end of the table. Please refer to Section 11.2.1 for Specimen Requirements.

Assessments	Prior to Day 1 of Each Cycle ^A	Every other week for first 8 weeks of study therapy (Arms II and III)	After completion or stopping of therapy ^B	Timed (Treatment Cycle Independent)
History and Physical	E		I	
Vital Signs (Blood Pressure, Heart Rate, Temperature and Pulse Oxygen Saturation)	F			
Performance Status	E			
Toxicity Assessment	E	F	I	
CBC/Differential/Platelets	G	F	I	O
Concomitant Medications ^N	E	F	I	
Serum chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, total protein	G		I	

Assessments	Prior to Day 1 of Each Cycle ^A	Every other week for first 8 weeks of study therapy (Arms II and III)	After completion or stopping of therapy ^B	Timed (Treatment Cycle Independent)
TSH ^C	G			H
CA-125	G		I	
Urinalysis or urine protein: creatinine ratio	G			
Electrocardiogram ^D	G			
MUGA or echocardiogram				J
Home blood pressure assessment	Please see footnote K			
Radiographic tumor measurement				L
Patient-reported outcome assessments				M

A: Timing of assessments prior to Cycle 1 Day 1 may be as per pre-treatment assessments schedule.

B: For patients in Arm I at the time of completion of therapy, and for patients in all arms who discontinue study therapy for non-progression events. These should be continued until time of progression or another therapy is initiated.

C: Should be performed pre-study and prior to the first two cycles of treatment for participants on Arm III. Additional assessment of thyroid function should be performed as clinically indicated.

D: Should be performed pre-study and prior to each cycle if clinically indicated

E: ≤ 1 day of treatment

F: Day of treatment/assessment

G: ≤ 3 days of treatment

H: 6 months (+/- 2 weeks) after stopping study treatment for participants on Arm III.

I: Every 9 weeks (+/- 7 days)

J: MUGA or echocardiogram should be performed at baseline for all patients at increased risk for compromised LVEF, including patients with prior treatment with anthracyclines, prior treatment with trastuzumab, prior central thoracic RT, or history of myocardial infarction within the 12 months prior. LVEF assessment by MUGA or echocardiogram should be performed on an every 16 week (+/- 7 days) basis for patients with these risk factors on Arm III of study treatment. Additionally, LVEF assessment by MUGA or echocardiogram should be performed every 12 weeks (+/- 7 days) while on treatment for participants receiving Arm I, Regimen III (carboplatin/pegylated liposomal doxorubicin).

K: Because of the rapid changes in blood pressure that can occur and the potential for severe life-threatening complications if hypertension is not appropriately managed, patients on Arm III should check their blood pressure twice daily for at least the first 8 weeks after starting study drug, or, if anti-hypertensive management is required, until a stable anti-hypertensive regimen has been established, even if this requires more than 8 weeks. After 8 weeks or once a stable regimen has been achieved, blood pressure monitoring may be reduced to once daily. Twice daily monitoring should be re-implemented after any cediranib hold/dosing delay for two weeks or until the patient is re-established on a stable anti-hypertensive regimen, whichever takes longer. Patient blood pressures should be reviewed with the study team on a weekly basis for the first 8 weeks of study treatment to ensure that blood pressure guidelines are being correctly followed.

L: Every 9 weeks (+/- 7 days) from cycle 1, day 1 (regardless of delays and/or changes in treatment schedule) for the first year; then every 12 weeks (+/- 7 days) thereafter until disease progression is confirmed; also repeat at any other time if clinically indicated based on symptoms or physical signs suggestive of new or progressive disease. An Excel tool is available on the CTSU website to calculate dates of re-imaging. Utilize **same** imaging modality as for pre-cycle 1 baseline assessment. Images from radiographic studies should be uploaded for future independent radiologic review via TRIAD Digital Image Submission as detailed in Appendix XIV.

M: Patient-reported outcomes should be performed every 12 weeks for 3 years, unless the patient withdraws from study participation. Patients who stop study treatment for any reason other than death or withdrawal should be assessed on schedule. PRO assessments should continue post-progression.

N: Because of a potential for interaction of cediranib and olaparib with other drugs through the cytochrome P450 system, special attention should be paid to other medications known to affect P450 isoenzymes, in particular CYP3A4. Please see Appendix V for a list of these medications.

O: For patients on Arm I, Regimen II (gemcitabine/carboplatin), CBC needs to be drawn for day 8 treatments.

4.3 Assessments After treatment (11/07/2016)

The following observations and tests are to be performed and recorded on the appropriate form(s). Vital status and patient-reported outcome assessments should be continued per the schedules noted below unless the patient withdraws from study participation. Please note: Each entry refers to the corresponding footnote at the end of the table.

Assessments	Timed
Vital Status	A
Toxicity Assessment	B
Radiographic tumor measurement	C
Patient-reported outcome assessments	D

A: Every 3 months for 2 years and then every 6 months for 3 years. Follow-up Forms are collected for the 5-year follow-up period or until study termination.

B: Report all adverse events that occur within 30 days of last protocol treatment on the Toxicity form for the last cycle of therapy administered. For reporting of delayed toxicity, see Section 7.

C: In the case that protocol directed therapy is discontinued for reasons other than disease progression, follow radiographic tumor measurement schedule as defined under Assessments During Treatment.

D: Patient-reported outcomes should be performed every 12 weeks for 3 years, unless the patient withdraws from study participation. PRO assessments should continue post-progression.

5.0 TREATMENT PLAN/Regimen description

Patients will be randomized to one of three treatment regimens in a 1:1:1 ratio, stratified by the following characteristics:

- a. Germline BRCA1/2 mutation status (deleterious or suspected deleterious versus non-deleterious)
- b. Prior angiogenic treatment for ovarian cancer (yes versus no)
- c. Prior platinum-free interval (6-12 months versus >12 months)

All participants must have a known germline BRCA1/2 mutation status prior to randomization. Participants who do not have a known BRCA1/2 mutation status by a CLIA-certified assay that includes at a minimum full sequencing of both BRCA1 and BRCA2 will be tested for germline mutation prior to randomization.

5.1 Arms/Regimens (11/07/2016)

Patients will be randomized to one of the following three arms in an open-label manner. Treatments will take place in an outpatient setting. Due to the differing schedules and routes of administration, patients on the reference regimen arm will not be blinded. Additionally the study will not be blinded with regards to whether patients are receiving single agent olaparib or combination cediranib/olaparib. See Appendix XIII for general treatment guidelines.

Because of the differences in cycle lengths between the allowed regimens, tumor reassessment will be time-based, and not cycle-based, with CT scan or MRI performed once every 9 weeks (+/- 7 days) for the first year and every 12 weeks (+/- 7 days) after the first year, and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Imaging assessments can be discontinued if disease progression is confirmed according to RECIST 1.1. However, if a patient discontinues study treatment for any reason other than progression, imaging studies should continue on the protocol-outlined schedule until progression. After 1 years of protocol therapy or follow-up (measured from approximately cycle 1, day 1), imaging studies will be conducted every 12 weeks. Excel tool will be provided to sites to assist in determining imaging dates.

No modification of the assigned regimens is allowed.

5.1.1 Arm I (Reference Regimen): Platinum-based chemotherapy (07/31/2017)

Patients randomized to the platinum-based chemotherapy arm may be treated with one of the three regimens specified in this section per investigator discretion (the planned regimen should be specified prior to randomization). Patients should receive treatment per standard practice and may continue on treatment until progression per investigator discretion if having continued response and/or clinical benefit. The number of cycles of therapy should be administered as clinically appropriate, although it is suggested that patients should receive at least 4 cycles of therapy. **After completion of chemotherapy, patients must be followed without further chemotherapy or maintenance therapy until disease progression**, defined as objective findings on imaging studies, and **not** progression of disease by CA125 alone. Maintenance therapy (e.g. with bevacizumab or a PARP inhibitor) is not allowed on this study.

Dosing for patients receiving one of the reference regimens should be recalculated for weight changes $\geq 10\%$ of baseline.

5.1.1.1 Regimen I:

A cycle will be 21 days in length, with paclitaxel and carboplatin infused IV as below on day 1. Paclitaxel infusion should occur prior to carboplatin infusion. Pre medications with dexamethasone, diphenhydramine, and famotidine (or other H2 blocker) should be administered prior to paclitaxel infusion per institutional or practice standards. Anti-emetics may be administered per institutional and practice standards.

- Paclitaxel (175mg/m²) IV infused over 3 hours on day 1
- Carboplatin (AUC 5 or 6) IV infused over 30-60 minutes on day 1

5.1.1.2 Regimen II:

A cycle will be 21 days in length, with gemcitabine infused IV on days 1 and 8 and carboplatin on day 1, as detailed below. Gemcitabine infusion should occur prior to carboplatin infusion on day 1. Anti-emetics may be administered per institutional and practice standards.

- Gemcitabine (1000mg/m²) IV infused over 30 minutes on days 1 and 8
- Carboplatin (AUC4) IV infused over 30-60 minutes on day 1

5.1.1.3 Regimen III: (11/07/2016)

A cycle will be 28 days in length, with pegylated liposomal doxorubicin (PLD) and carboplatin infused IV on day 1, as detailed below. PLD infusion should occur prior to carboplatin infusion. Anti-emetics may be administered per institutional and practice standards.

- Pegylated liposomal doxorubicin (30mg/m²) IV on day 1 per institutional standard.
- Carboplatin (AUC5) IV infused over 30-60 minutes on day 1

5.1.2 Arm II: Olaparib monotherapy (11/07/2016)

Olaparib 300mg in tablet formulation orally twice daily continuous dosing. Olaparib tablets should be taken twice a day approximately 12 hours apart.

One cycle will be considered 28 days. Cycle days are continuously numbered regardless of any dose holds or interruptions. Patients will remain on treatment until disease progression. Patients randomized to Arm II will be required to maintain a medication diary (found in Appendix VII).

5.1.3 Arm III: Olaparib and cediranib (11/07/2016)

Olaparib 200mg in tablet formulation orally twice daily continuous dosing. Olaparib tablets should be taken twice a day approximately 12 hours apart.

Cediranib 30mg in tablet formulation orally once daily. Cediranib should be taken on an empty stomach in the morning approximately 1 hour before taking the morning dose of olaparib.

One cycle will be considered 28 days. Cycle days are continuously numbered regardless of any dose holds or interruptions. Patients will remain on treatment until disease progression. Patients randomized to Arm III will be required to maintain medication and blood pressure diaries (found in Appendix VIII and IX). A blood pressure cuff will be provided to patients randomized to Arm III.

5.2 Duration of Study

5.2.1 Patients on the reference arm (Arm I) of the study will receive platinum-based chemotherapy as outlined. The number of cycles will be per the investigator's discretion. After completion of chemotherapy, patients will continue on active surveillance until disease progression. Patients on Arms II and III of the study will continue on study treatment until disease progression, or adverse events, require discontinuing protocol treatment. All patients will continue to be followed after disease progression or discontinuation of protocol treatment for PROs. The patient may voluntarily withdraw from the study at any time.

5.2.2 All patients will be followed for disease status and toxicity (with completion of all required case report forms) until death or voluntary withdrawal from study. In addition, following study therapy, patients will continue with imaging studies until the time of progression as well as continued PRO assessments.

5.2.3 Adequate Duration of Study to Evaluate Toxicity. All patients who initiate any study therapy will be evaluated for toxicity

5.3 Follow-up after study treatment discontinuation and/or progression

The median PFS reported in studies with platinum-based doublets in women with recurrent platinum-sensitive ovarian cancer ranges between 8.4 months to 13 months (2-4, 8, 10). The primary analysis of PFS will be a stratified log-rank test and intention-to-treat (ITT) with patients analyzed according to the arm to which they were randomized, regardless of whether treatment is received.

To allow for better understanding of time to subsequent therapy and PFS2, patients will be followed after progression on study treatment, with data capture to include the date of initiation of the subsequent therapy, detailed information on the type of subsequent therapy received, and time to progression on the subsequent therapy.

6.0 TREATMENT MODIFICATIONS/MANAGEMENT

For AEs that are unrelated to the study drugs, study treatment may be held for up to 14 days at the discretion of the treating investigator. Drug holds of greater than 14 days for unrelated AEs where the patient is experiencing ongoing clinical benefit may be considered after discussion with the overall PI.

6.1 Reference regimens (Arm I)

6.1.1 Hematologic toxicity

6.1.1.1 Use of hematopoietic agents

Myeloid growth factors (filgrastim or pegfilgrastim) may be used per institutional standards. It is recommended that NCCN and/or ASCO guidelines be consulted. Filgrastim should be administered subcutaneously starting 24 to 72 hours after the last dose of chemotherapy and continuing through hematopoietic recovery, but should not be administered within the 48 hours preceding the next dose of cytotoxic chemotherapy. Pegfilgrastim should be administered at 6mg subcutaneously 24 to 72 hours after the last dose of chemotherapy and should not be administered within 2 weeks preceding the next dose of cytotoxic chemotherapy. Pegfilgrastim should not be used for patients receiving chemotherapy that is given less than every 2 weeks.

Use erythropoietin-stimulating agents per standard of care National Comprehensive Cancer Network (NCCN) and/or institutional guidelines, iron supplements, and/or transfusions as clinically

indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.

Patients should not receive thrombopoietic agents. Transfusions may be administered as clinically indicated for management of anemia.

6.1.1.2 Arm I, Regimen I: Carboplatin and paclitaxel

Day 1 of any given cycle of Regimen I should not be administered unless the ANC is $\geq 1,500/\text{mcL}$ and the platelet count is $\geq 100,000/\text{mcL}$. Treatment may be delayed for a maximum of 3 weeks until these parameters are met. If patient counts fail to recover adequately within three weeks, discontinue protocol-directed therapy.

Dose modifications may occur for neutropenic or thrombocytopenic events, as detailed in the following tables. Dose modifications should be carried through to future cycles of therapy once performed.

Table 6.1.1.2.A: Dose modifications for neutropenia, Regimen I		
	<u>Hematologic Event</u>	<u>Dose Modification</u>
Initial Occurrence	Febrile neutropenia [†] Grade 4 neutropenia lasting ≥ 7 days ANC $< 1000/\text{mcL}$ on Day 1 Treatment delay > 7 days for neutropenia	Reduce carboplatin by 1 AUC Initiate G-CSF if not already receiving
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce carboplatin by 1 AUC ^{††} Reduce paclitaxel dose to $135\text{mg}/\text{m}^2$
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue patient from protocol-directed therapy
[†] Febrile neutropenia is defined within the CTCAE as a disorder characterized by an ANC $< 1000/\text{mcL}$ and a single temperature of > 101 degrees F or a sustained degree of ≥ 100.4 degrees F for more than an hour.		

††Carboplatin may not be reduced below AUC4. If neutropenic event occurs at a carboplatin AUC of 4, carboplatin dosing should be maintained at AUC4 and paclitaxel dose reduced to 135mg/m2.

	Hematologic Event	Dose Modification
Initial Occurrence	Any occurrence of grade 4 thrombocytopenia (platelets < 25,000/mcL) Grade 3 thrombocytopenia with bleeding event (platelets 25,000 to <50,000/mcL) Platelets < 75,000/mcL on Day 1† Treatment delay > 7 days for thrombocytopenia	Reduce carboplatin by 1 AUC
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce carboplatin by 1 AUC†† Reduce paclitaxel dose to 135mg/m2
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue patient from protocol-directed therapy
† At the discretion of the investigator, a dose reduction may be performed for platelet counts < 100,000/mcL on Day 1. ††Carboplatin may not be reduced below AUC4. If a thrombocytopenic event occurs at a carboplatin AUC of 4, carboplatin dosing should be maintained at AUC4 and paclitaxel dose reduced to 135mg/m2.		

6.1.1.3 Arm I, Regimen II: Carboplatin and gemcitabine

Day 1 of any given cycle of Regimen I should not be administered unless the ANC is $\geq 1,500/\text{mcL}$ and the platelet count is $\geq 100,000/\text{mcL}$. Treatment may be delayed for a maximum of 3 weeks until these parameters are met. Patients who fail to recover adequate counts within a three-week delay should discontinue protocol-directed cytotoxic therapy. Day 8 treatment should be administered per the guidelines in Table 6.1.1.3.A below, and dose modifications for hematologic events should be performed per Table 6.1.1.3.B.

Treatment Day	ANC (per mcL)		Platelet count (per mcL)	% of full dose
Day 1	≥ 1500 < 1500	and or	$\geq 100,000$ < 100,000	100% Delay treatment cycle
Day 8	≥ 1500 1000-1499	and or	$\geq 100,000$ 75,000-99,999	100% 50%

	< 1000	or	< 75,000	Hold
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Table 6.1.1.3.B: Dose modifications for hematologic toxicity, Regimen II		
	<u>Hematologic Event</u>	<u>Dose Modification</u>
Initial Occurrence	Febrile neutropenia [†] ANC < 500/mcL for > 5 days ANC < 100/mcL for > 3 days Grade 4 thrombocytopenia (platelets < 25,000/mcL) Grade 3 thrombocytopenia with bleeding event (platelets 25,000 to <50,000/mcL) Treatment delay > 7 days for neutropenia or thrombocytopenia	Permanently reduce gemcitabine to 800mg/m ² on Days 1 and 8 Initiate G-CSF for neutropenic events if not already receiving
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Permanently reduce gemcitabine dose to 800mg/m ² on Day 1 only (Day 8 gemcitabine is permanently omitted)
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue patient from protocol-directed therapy
[†] Febrile neutropenia is defined within the CTCAE as a disorder characterized by an ANC <1000/mcL and a single temperature of >101 degrees F or a sustained degree of ≥ 100.4 degrees F for more than an hour.		

6.1.1.4 Arm I, Regimen III: Carboplatin and pegylated liposomal doxorubicin (PLD)

Day 1 of any given cycle of Regimen III should not be administered unless the ANC is ≥ 1,500/mcL and the platelet count is ≥ 100,000/mcL. Treatment may be delayed for a maximum of 3 weeks until these parameters are met. Patients who fail to recover adequate counts within a three-week delay should discontinue protocol-directed cytotoxic therapy.

Dose modifications may occur for neutropenic or thrombocytopenic events, as detailed in the following tables. Dose modifications should be carried through to future cycles of therapy once performed.

Table 6.1.1.4.A: Dose modifications for neutropenia, Regimen III		
	<u>Hematologic Event</u>	<u>Dose Modification</u>
Initial Occurrence	Febrile neutropenia [†] Grade 4 neutropenia lasting ≥ 7 days ANC < 1000/mcL on Day 1	Reduce carboplatin by 1 AUC Initiate G-CSF if not already receiving

	Treatment delay > 7 days for neutropenia	
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce PLD dose to 25mg/m ²
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue patient from protocol-directed therapy
[†] Febrile neutropenia is defined within the CTCAE as a disorder characterized by an ANC <1000/mcL and a single temperature of >101 degrees F or a sustained degree of ≥ 100.4 degrees F for more than an hour.		

Table 6.1.1.4.B: Dose modifications for thrombocytopenia, Regimen III		
	Hematologic Event	Dose Modification
Initial Occurrence	Grade 4 thrombocytopenia (platelets < 25,000/mcL) Grade 3 thrombocytopenia with bleeding event (platelets 25,000 to <50,000/mcL) Platelets < 100,000/mcL on Day 1 [†] Treatment delay > 7 days for thrombocytopenia	Reduce carboplatin by 1 AUC
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce PLD dose to 25mg/m ²
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue patient from protocol-directed therapy
[†] At the discretion of the investigator, a dose reduction may be performed for platelet counts < 100,000/mcL on Day 1.		

6.1.2 Non-hematologic toxicity

Management of non-hematologic toxicities on the reference arm should be per institutional practice and guidelines. Criteria for dose holds and modifications on the reference arms for non-hematologic toxicity should follow institutional practice and prescribing information. Permanent dose reductions should follow dose levels as outlined in Table 6.1.2.A. Dose modifications for alopecia, nausea, or constipation are not recommended. If treatment is delayed for greater than 3 weeks due to a drug-related non-hematologic toxicity, the patient may be discontinued from protocol-directed therapy after consultation with the Study Chair.

Table 6.1.2.A: Guidelines for permanent dose reductions, Reference Regimens		
Drug	First reduction	Second reduction
Carboplatin [†]	Decrease AUC by 1	Decrease AUC by 1

Paclitaxel	Decrease dose to 135 mg/m ²	Decrease dose to 110 mg/m ²
Gemcitabine	Decrease dose to 800mg/m ² on Days 1 and 8	Discontinue Day 8 dosing
Pegylated liposomal doxorubicin	Decrease dose to 25mg/m ²	Decrease dose to 20mg/m ²
†Carboplatin dose should not be reduced below an AUC of 4. Patients requiring a dose reduction below AUC4 should be removed from protocol-directed therapy.		

6.1.3 Hypersensitivity reactions (11/07/2016)

Of note, the occurrence of a hypersensitivity reaction may not be a dose-limiting toxicity. Depending on the severity of their hypersensitivity reaction, patients experiencing a hypersensitivity reaction may be retreated at full doses under institutional protocols to prevent hypersensitivity reactions. The below table provides recommendations regarding approach to continued treatment for patients experiencing hypersensitivity reactions. Sites may also follow institutional guidelines for prevention and/or avoidance of hypersensitivity reactions.

<u>Grade</u>	<u>Definition</u>	<u>Recommended treatment and management</u>
Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated	May consider retreatment per institutional guidelines. May consider pre-medication with steroids, antihistamines (diphenhydramine), or H2 blockers.
Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs.	Stop infusion immediately. May consider retreatment or desensitization, per institutional guidelines. Patients may be discontinued from protocol-directed therapy at the discretion of the investigator.
Grade 3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequel	Stop infusion immediately. May consider rechallenge under desensitization protocol, per institutional guidelines. Patients may be discontinued from protocol-directed therapy at the discretion of the investigator.
Grade 4	Life-threatening consequences; urgent intervention indicated.	Do not rechallenge. Protocol-directed therapy should be discontinued.

6.2 Arms II (olaparib) and III (olaparib and cediranib) (07/31/2017)

Arm II

Dose Level	Olaparib tablets
1	300 mg twice daily
-1	250 mg twice daily
-2	200 mg twice daily
-3	150 mg twice daily

Arm III

The dose levels and the general approach to dose modification of olaparib and cediranib combination therapy are shown below. AEs should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the case report form.

Dose Level	Olaparib tablets
1	200 mg twice daily
-1	150 mg twice daily
-2	100 mg twice daily

Dose level	Cediranib tablets
1	30 mg daily
-1	20 mg daily
-2	15 mg daily

For Arm III, 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. 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 overall study chair**, 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 overall study chair**.

For AEs that are unrelated to the study drugs, study drug may be held for up to 14 days at the discretion of the treating investigator. Drug holds of greater than 14 days for unrelated AEs where the patient is experiencing ongoing clinical benefit may be considered after discussion with the overall PI.

6.2.1 Hematologic toxicity

6.2.1.1 Use of hematopoietic agents

Use of hematopoietic agents will not be allowed in Arms II and III.

6.2.1.2 Dose modifications

Dose modifications for hematologic events on these arms should be managed per the following table.

Table 6.2.1.2.A: Dose Modification and Management of Hematologic Adverse Events, Arms II and III	
Hematologic Event	Dose Modification
Absolute neutrophil count \geq 1500/mcL AND Platelets \geq 100,000/mcL AND Hemoglobin \geq 8 mg/dL	Maintain dose level
Absolute neutrophil count $<$ 1500/mcL OR Platelets $<$ 100,000/mcL OR Hemoglobin $<$ 8 mg/dL	Hold treatment for up to 14 days until absolute neutrophil count \geq 1500/mcL, platelets \geq 100,000/mcL, and hemoglobin \geq 8 mg/dL. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.2. For patients whose treatment is held for ANC between 1000 and 1500/mcL, treatment may be resumed at the prior dose level, at the treating investigator's discretion. Patients whose counts have not recovered to absolute neutrophil count \geq 1500/mcL, platelets \geq 100,000/mcL, and hemoglobin \geq 8 mg/dL after 14 days should be removed from study.
Grade 4 hematologic AE related to cediranib or olaparib that does not resolve to absolute neutrophil count \geq 1500/mcL, platelets \geq 75,000/mcL, and hemoglobin \geq 8 mg/dL despite maximum supportive care after 14 days.	Remove patient from study.

Patients who have treatment held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery. If counts do not improve to CTCAE grade 1 or better despite drug cessation for 4 weeks, patients should be referred to a hematologist for further assessment. A bone marrow analysis should be considered per hematology assessment.

6.2.2 Non-hematologic toxicity

The management of general adverse events not otherwise specified in the following sections should be as per Table 6.2.2.A below. Management of specific toxicities, including hypertension, diarrhea, proteinuria, decrease in

LVEF, thyroid toxicities, and RPLS should be as further outlined in the below specific subsections and not per Table 6.2.2.A.

Table 6.2.2.A: General Management of Non-Hematologic Toxicity, Regimens II and III	
Observation	Action
AE resolves promptly with supportive care	Maintain dose level
Any \geq grade 3 non-hematologic (excluding grade 3 fatigue or easily correctable asymptomatic grade 3 laboratory abnormalities)	Hold study drug(s) ¹ for up to 14 days until toxicity resolves to \leq grade 1. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.2. ²
Any grade 2 non-hematologic AE or grade 3 fatigue related to cediranib or olaparib that persists despite maximal support.	Hold study drug(s) ¹ for up to 14 days until toxicity resolves to \leq grade 1. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.2. ² Patients whose toxicity has not resolved after 14 days will be removed from study.
1. Grade 3 or 4 non-hematologic AE related to cediranib and olaparib combination that does not resolve to grade 0-2 within 14 days despite maximum supportive care after treating patient at the lowest reduced dose level. ³ 2. Grade 3 or 4 non-hematologic AE related to cediranib/olaparib lasting > 14 days despite maximum supportive care and treatment being held.	Remove patient from protocol-specified treatment.
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 continued 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 reduced dose level may have their drug resumed at that dose level after discussion with the Study Chair if evidence of clinical benefit. ³ For thromboembolic events, treatment may be resumed at the discretion of the investigator once patient is asymptomatic.	

6.2.2.1 Hypertension

Table 6.2.2.1.A: Hypertension Monitoring and Management
<ul style="list-style-type: none"> • See Appendix III for suggested antihypertensive medications by class • Abbreviations: Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARB), selective beta blockers (BB), Dihydropyridine calcium channel blockers (DHP-CCP) • If patients require a delay of >2 weeks for management of hypertension, discontinuation of cediranib or protocol therapy may be considered after discussion with the Study Chair. • Patients may have up to 4 drugs for management of hypertension prior to any dose reduction in cediranib

<ul style="list-style-type: none"> Hypertension should be graded using the NCI CTCAE. Please note: patients may have baseline hypertension meeting CTCAE grading criteria on study entry. Should patients require increase in dosing of BP medication or increased number of medications, they should then be noted to have hypertension related to study drug, with grading as per CTCAE criteria. Baseline grade of hypertension should also be recorded in the patient's record. <u>Note:</u> Stopping or reduce the dose of cediranib is expected to cause a decrease in BP. <u>The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly.</u> 				
Event	Definition	Antihypertensive Therapy	Blood Pressure Monitoring	Cediranib Dose Modification
Grade 1	Asymptomatic transient (<24 hours) increase by >20 mmHg diastolic or to \geq 140/90 mmHg if previously WNL	Consider early initiation of BP medication for BP > 140/90 mmHg that is confirmed on a second reading. Cediranib can cause rapid escalation in BP, and early initiation of BP management can reduce likelihood of HTN-related complications.	Continue standard BP monitoring per treating MD and confirm resolution of BP to <140/90 mmHg within 24 hours.	None
Grade 2	Recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to \geq 140/90 mmHg if previously WNL Monotherapy may be indicated	Initiate BP medication for first line treatment. <i>Suggestions:</i> ACE-inhibitor Escalate dose of medication in step-wise 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. Study drug does not need to be held unless otherwise clinically necessary <i>Consider renal</i>	Increase frequency of monitoring until stabilized to BP <140/90 mmHg	Do not hold cediranib unless otherwise clinically necessary

		<i>consult</i>		
Grade 3	Requiring more than one drug or more intensive therapy than previously.	<p>Maximize 2 drug regimen</p> <ul style="list-style-type: none"> • <i>Suggestions:</i> ACE-inhibitor + BB <p>Escalate doses of existing medication until BP is controlled or at a maximum dose.</p> <p>If BP is not controlled to < 140/90 mmHg with two drug regimen, then add a third agent.</p> <p>Study Drug will not be held during trial of two drug combinations. Additional anti-hypertensive drugs, up to a total of 4, may be maximized for blood pressure control</p> <p><i>Consider consult with a blood pressure management specialist if greater than 3 drugs are required for BP control.</i></p>	Increase frequency of monitoring until stabilized to BP <140/90 mmHg	<p>Do not hold cediranib or other study drugs unless BP is not decreased to less than 150/100 mmHg 48 hours after multi-drug therapy is instituted or if clinical symptoms worsen (e.g. headache).</p> <p>If BP is not controlled to less than 150/100 mmHg with maximal therapy or if clinical symptoms worsen, then hold cediranib (up to 14 days) until maximum effect of the anti-hypertensive agents is achieved.</p> <p>If BP is reduced to less than 140/90 within 14 days, cediranib may be resumed at prior dose.</p>
Grade 4	<p>If threatening consequences</p> <p>OR</p> <p>SBP ≥ 180mmHg</p> <p>OR</p>	<p>Initiate treatment</p> <p>Hospitalize patient for ICU management, IV therapy as necessary</p> <p>14 days are allowed to maximize the full</p>	Intensive BP monitoring (hospitalization if necessary)	<p>Hold cediranib.</p> <p>If BP is reduced to less than 140/90 within 14 days, cediranib may be resumed at a reduced dose after discussion with the</p>

	DBP \geq 110mmHg	effect of anti-hypertensive agents.		Study PI and/or sponsor.
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6.2.2.2 Diarrhea

Diarrhea is often observed with cediranib, and active and early management of diarrhea is recommended even with grade 1 diarrhea. Management as follows:

Table 6.2.2.2.A: Management of Diarrhea	
Toxicity	Management/Modifications
Initial grade 1 or 2 diarrhea:	Patients can take loperamide (per standard practice) and continue to take loperamide until patients are free from diarrhea for at least 12 hours. The dose of loperamide should not exceed 16mg in a 24-hour period. Patients should also be counseled to start a BRAT (bananas, rice, applesauce, toast) diet.
	If diarrhea persists despite 24 hours of loperamide treatment, hold cediranib for a maximum of 7 days, continue loperamide, and maintain hydration. Cediranib may be restarted at the same dose once patients have been free from diarrhea for 12 hours.
For either persistent grade 2 diarrhea or grade 3 or 4 diarrhea:	Follow 6.2.2.A

6.2.2.3 Proteinuria

Although patients with $\geq 1+$ proteinuria or UPC > 1.0 at entry are ineligible, increases in proteinuria may occur during treatment and should be managed as follows:

Table 6.2.2.3.A: Management of Proteinuria		
Proteinuria Value if following by U/A	Monitoring	Dose modification
<u>Greater than 2+</u> on urine dipstick or U/A AND Creatinine $\leq 1.5x$ ULN	Perform UPC.	<u>Continue study drugs at planned dose, and see below.</u>

<u>Greater than 2+ on urine dipstick or U/A AND Creatinine >1.5x ULN</u>	Perform UPC.	HOLD cediranib until results of UPC are known, and see below
Based on results of the UPC[†]:		
UPC ≤ 1.0	Continue monitoring prior to each cycle as per previous.	Continue study drugs at planned dose.
UPC > 1.0 and ≤ 3.5 AND Creatinine ≤ 1.5x ULN	Perform UPC prior to each cycle.	Continue study drugs at planned dose.
UPC > 3.5 OR Creatinine > 1.5x ULN	Perform UPC prior to each cycle.	Hold cediranib for up to 7 days and repeat UPC and Creatinine assessment. If UPC resolves to <3.5 and Creatinine to ≤ 1.5x ULN, resume cediranib with reduction in cediranib by one dose level. Consider consultation with nephrologist.
†If UPC is <1.0 and creatinine >1.5x ULN, AE management should be followed as per Table 6.2.2.2.3A		

6.2.2.4 Thyroid toxicities

The use of cediranib has been associated with elevations of the thyroid stimulating hormone (TSH) and patients should be managed as per the following table. In all cases, study treatment should continue unless clinically contraindicated. Referral to an endocrinologist should also be considered if thyroid abnormalities occur.

Table 6.2.2.4.A: Monitoring and Management of Thyroid Toxicities	
Result of TSH, T4, and T3	Action
Increases of TSH with normal T4/T3:	Monitor
Increases in TSH with normal T4/T3 and adverse events suggestive of incipient hypothyroidism:	Consider replacement thyroxine.
Increase in TSH with reductions in T4 and T3:	Consider replacement thyroxine.

6.2.2.5 Decrease in LVEF (11/07/2016)

Patients randomized to Arm III who have any of the following should undergo an echocardiogram or MUGA at baseline and every four cycles (16 weeks) while on study:

- a. Prior treatment with anthracyclines
- b. Prior treatment with trastuzumab
- c. Prior central thoracic radiation therapy (RT), including RT to the heart
- d. History of myocardial infarction within 6 to 12 months (Patients with history of myocardial infarction within 6 months are excluded from the study)

The decision to continue or hold cediranib/olaparib is based on the LVEF as it relates to the institution's lower limit of normal (LLN) and change in ejection fraction from screening (LVEF as measured at registration) according to the following table:

Relationship of LVEF to Institution's LLN	LVEF Decrease < 10%	LVEF Decrease 10-15%	LVEF Decrease ≥ 16%
Normal	Continue	Continue	Continue and repeat MUGA/ECHO within 1-2 cycles
1-5% below LLN	Continue and repeat MUGA/ECHO within 1-2 cycles	Continue and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles
≥ 6% below LLN	Continue and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles

6.2.2.6 Posterior Reversible Encephalopathy Syndrome (PRES)

Cediranib and olaparib should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Study drugs should not be resumed without consultation with the Study Chair. After consultation with the Study Chair and the NCI, consideration of restarting the study may be evaluated in light of any clinical benefit.

7.0 ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents (11/07/2016)

Investigational Agents

The investigational agents administered in NRG-GY004, cediranib and olaparib are being made available under an IND sponsored by CTEP. For patients on Arm II or III receiving cediranib and olaparib, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in **Section 7.5.2.1** of the protocol.

Commercial Agents

The commercial agents in NRG-GY004 are carboplatin, paclitaxel, pegylated liposomal doxorubicin, and gemcitabine. For patients on Arm I receiving only commercial agents, determination of whether an adverse event meets the expedited reporting criteria, see the reporting table in **Section 7.5.2.2** of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Comprehensive Adverse Events and Potential Risks (CAEPR) List for Study Agents

7.3.1

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Cediranib (AZD2171, NSC 732208)

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/aeguidelines.pdf for further clarification. *Frequency is provided based on 1608 patients.* Below is the CAEPR for Cediranib (AZD2171).

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 2.15, November 7, 2018¹

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
ENDOCRINE DISORDERS			
	Hyperthyroidism		
	Hypothyroidism		<i>Hypothyroidism (Gr 2)</i>
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<i>Abdominal pain (Gr 3)</i>
	Anal mucositis		<i>Anal mucositis (Gr 2)</i>
	Constipation		<i>Constipation (Gr 3)</i>
Diarrhea			<i>Diarrhea (Gr 3)</i>
	Dry mouth		<i>Dry mouth (Gr 2)</i>
	Dysphagia		<i>Dysphagia (Gr 2)</i>
		Gastrointestinal fistula ²	
		Gastrointestinal perforation ³	
	Mucositis oral		<i>Mucositis oral (Gr 3)</i>
Nausea			<i>Nausea (Gr 3)</i>
		Pancreatitis	
	Rectal mucositis		<i>Rectal mucositis (Gr 2)</i>
	Small intestinal mucositis		<i>Small intestinal mucositis (Gr 2)</i>
	Vomiting		<i>Vomiting (Gr 3)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			<i>Fatigue (Gr 3)</i>
HEPATOBIILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Infection ⁴		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		<i>Alanine aminotransferase increased (Gr 3)</i>
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		<i>Aspartate aminotransferase increased (Gr 3)</i>
	Lymphocyte count decreased		
	Neutrophil count decreased		
	Platelet count decreased		

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Thyroid stimulating hormone increased		<i>Thyroid stimulating hormone increased (Gr 2)</i>
	Weight loss		<i>Weight loss (Gr 2)</i>
METABOLISM AND NUTRITION DISORDERS			
Anorexia			<i>Anorexia (Gr 3)</i>
	Dehydration		<i>Dehydration (Gr 3)</i>
	Hypophosphatemia		<i>Hypophosphatemia (Gr 3)</i>
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Generalized muscle weakness		
NERVOUS SYSTEM DISORDERS			
	Dizziness		<i>Dizziness (Gr 2)</i>
	Headache		<i>Headache (Gr 3)</i>
	Lethargy		
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Nephrotic syndrome	
	Proteinuria		<i>Proteinuria (Gr 2)</i>
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		<i>Cough (Gr 2)</i>
	Dyspnea		<i>Dyspnea (Gr 3)</i>
	Laryngeal mucositis		<i>Laryngeal mucositis (Gr 2)</i>
	Pharyngeal mucositis		<i>Pharyngeal mucositis (Gr 2)</i>
	Tracheal mucositis		<i>Tracheal mucositis (Gr 2)</i>
Voice alteration			<i>Voice alteration (Gr 2)</i>
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia syndrome		<i>Palmar-plantar erythrodysesthesia syndrome (Gr 2)</i>
VASCULAR DISORDERS			
		Arterial thromboembolism	
Hypertension			<i>Hypertension (Gr 3)</i>
	Thromboembolic event		<i>Thromboembolic event (Gr 4)</i>
	Vascular disorders - Other (hemorrhage) ⁵		

¹This 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.

²Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

³Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

⁴Infections includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

⁵Hemorrhage is a known consequence of VEGF/VEGFR signaling inhibition. The majority of hemorrhage events reported were mild; however, serious events, defined as symptomatic bleeding in a critical area or organ system (e.g., eye, gastrointestinal tract, genitourinary [GU] tract, respiratory tract, and nervous system) have been reported.

Adverse events reported on cediranib (AZD2171) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that cediranib (AZD2171) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (polycythemia); Bone marrow hypocellular; Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (premature ventricular complexes); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Mobitz (type) II atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ears feel full/plugged); Ear and labyrinth disorders - Other (viral labyrinthitis); Tinnitus; Vertigo

EYE DISORDERS - Blurred vision; Eye disorders - Other (blindness); Eye disorders - Other (visual disturbance); Papilledema; Photophobia; Retinal vascular disorder

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Bloating; Colitis; Colonic obstruction; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Flatulence; Gastric necrosis; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (hydrops); Gastrointestinal disorders - Other (tongue sensitivity); Ileus; Oral pain; Periodontal disease; Peritoneal necrosis; Rectal pain; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Fever; Gait disturbance; Hypothermia; Malaise; Non-cardiac chest pain; Pain

HEPATOBIILIARY DISORDERS - Cholecystitis; Gallbladder obstruction; Hepatic pain; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice cholestatic)

IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Immune system disorders - Other (systemic inflammatory response syndrome)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture; Injury, poisoning and procedural complications - Other (tracheostomy malfunction); Intestinal stoma leak; Venous injury; Wound dehiscence

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Hemoglobin increased; INR increased; Investigations - Other (elevated ammonia level); Investigations - Other (increased blood erythropoietin); Lipase increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Avascular necrosis; Back pain; Bone pain; Chest wall pain; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Myalgia; Myositis; Neck pain; Pain in extremity; Rotator cuff injury

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Central nervous system necrosis; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Encephalopathy; Hydrocephalus; Ischemia cerebrovascular; Memory impairment; Muscle weakness left-sided; Nervous system disorders - Other (coma); Nervous system disorders - Other (right hemiparesis); Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Spinal cord compression; Stroke; Syncope; Transient ischemic attacks; Tremor

PSYCHIATRIC DISORDERS - Confusion; Delirium; Depression; Hallucinations; Insomnia; Suicide attempt

RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Cystitis noninfective; Hematuria; Urinary retention; Urinary tract obstruction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Menorrhagia; Vaginal fistula

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fistula; Pulmonary hypertension; Sinus pain

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pruritus; Purpura; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (petechiae); Skin and subcutaneous tissue disorders - Other (plantar warts); Skin ulceration; Urticaria

VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hypotension; Vasculitis

Note: Cediranib (AZD2171) 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.

7.3.2 Adverse Effects

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/aeguidelines.pdf for further clarification. *Frequency is provided based on 2073 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 2.4, April 24, 2019¹

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 2073]			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)
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		Abdominal pain (Gr 2)
	Constipation		Constipation (Gr 2)
Diarrhea			Diarrhea (Gr 2)
	Dyspepsia		Dyspepsia (Gr 2)
Nausea			Nausea (Gr 3)
Vomiting			Vomiting (Gr 3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			Fatigue (Gr 3)
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection ²		
INVESTIGATIONS			
	Creatinine increased		
	Lymphocyte count decreased		
	Neutrophil count decreased		
	Platelet count decreased		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			Anorexia (Gr 2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
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	

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.

¹This 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.

²Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATION SOC.

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 - Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Tinnitus

ENDOCRINE DISORDERS - Hypothyroidism

GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Mucositis oral; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Non-cardiac chest pain

IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - 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; 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 cramp; Muscle weakness lower limb; Myalgia; Neck pain; Pain in extremity; Rotator cuff injury

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; 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; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Pruritus; Rash maculo-papular

VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; 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.

7.4 Adverse Events for Commercial Study Agents

Refer to the package insert for detailed pharmacologic and safety information.

7.5 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site,

<https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613>

Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the CTEP as the IND sponsor for this study by telephone at 301-897-7497 and to NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.5.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 3 days. Supporting source documentation is requested by CTEP as the IND sponsor for this study and NRG as needed to complete adverse event review. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the CTEP at 301-230-0159 and NRG Regulatory Affairs at 215-854-0716.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as “an action *not* recommended” must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the “NOT recommended” assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.5.2 Expedited Reporting Requirements for Adverse Events (11/07/2016)

7.5.2.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention¹

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 CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	7 Calendar Days		

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:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

7.5.2.2 Phase 1, 2 and 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a non-IND/IDE within 30 Days of the Last Administration of the Commercial Agent/Intervention ¹

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 commercial agent(s)/intervention

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 NRG via CTEP-AERS within 24 hours of learning of the AE, followed by a complete report within 3 calendar days of the initial 24-hour report.

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

Expedited AE reporting timelines are defined as:

- o “24-Hour; 3 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.

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

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

- All Grade 3, 4, and Grade 5 AEs
- Grade 1 and 2 AEs resulting in hospitalization or prolongation of hospitalization

7.5.3 Reporting to the Site IRB/REB (11/07/2016)

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.4 Secondary Malignancy (11/07/2016)

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 during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported 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.

Second Malignancy:

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

- 7.5.4 Reporting to the Pharmaceutical Company: As the IND Sponsor, CTEP/DCTD will assume the responsibility of forwarding CTEP-AERS reports to the pharmaceutical collaborator as needed.

8.0 REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

8.1 Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed **Statement of Investigator Form** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed **Supplemental Investigator Data Form** (IDF)
- a completed **Financial Disclosure Form** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at

<http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>.

For questions, please contact the **CTEP Investigator Registration Help Desk** by email at <pmbregpend@ctep.nci.nih.gov>.

8.1.1 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For

questions, please contact the *CTEP Associate Registration Help Desk* by email at <ctepreghelp@ctep.nci.nih.gov>.

8.1.2 Site Registration Requirements (11/07/2016) (07/31/2017)

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

8.1.2.1 IRB Approval:

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. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at <https://www.ctsu.org>. For sites under the CIRB initiative, IRB data will automatically load to RSS.

8.1.2.2 Downloading Site Registration Documents:

Site registration forms may be downloaded from the NRG-GY004 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS. Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password. Click on the Protocols tab in the upper left of your screen. Click on the *NCTN NRG* link to expand, then select trial protocol NRG-GY004. Click on the Site Registration Documents link.

8.1.2.3 Site Specific Requirements for NRG-GY004 Site Registration:

All the requirements listed below must be completed and submitted to the CTSU before the site can be activated.

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- IRB approved Informed Consent
- Toxicity Management Training Site Initiation Visit (SIV)*

***Toxicity Management Training SIV**

All institutions participating in this trial will be required to participate in a Toxicity Management Training SIV. This training will focus on the toxicities and the toxicity management around cediranib. One investigator and one study coordinator/nurse from each site must attend an SIV to satisfy the regulatory requirement. This is an institution specific requirement to participate in this trial. Scheduled trainings and details for participation are on the NRG-GY004 CTSU web site. NRG Oncology will notify CTSU when an institution has satisfied this requirement.

8.1.2.4 Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval *and Model Informed Consent* to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office

1818 Market Street, Suite 1100

Philadelphia, PA 19103

Phone: 1-866-651-2878

Fax: 215-569-0206

E-mail: CTSURegulatory@ctsu.cocccg.org (for regulatory document submission only)

8.1.2.5 Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

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

8.1.3 **Investigator Pre-registration Requirements (11/07/2016)**

- Documentation of the Principal Investigator's and co-investigators' GCP Training through Firecrest or another valid GCP training course
- Documentation of the Principal Investigator's and co-investigators' protocol-specific training through Firecrest

OPEN will not allow an investigator to enroll a patient until the investigator specific training requirements have been satisfied.

To Obtain Firecrest Access

To request investigator and/or other staff access to Firecrest, please complete the excel document entitled “Firecrest Site and User Master Spreadsheet”, that is on the CTSU web site under the “LPO” tab.

When completed, submit to NRG-GY-Regulatory@nrگونcology.org with the following subject line in the e-mail:

[Study Number(s)] – Request for Firecrest Access [NCI CTEP Institution Code(s)]

Failure to include the above subject line, may delay the request.

The following fields in the spreadsheet must be completed:

- Study*
- Country*
- Site Number (NCI CTEP Institution Code)
- Institution Name
- Title*
- First Name
- Last Name
- Role*
- Email address

*These fields have a drop down list of valid entries for selection

Within 24 hours of receipt, the Regulatory Affairs Department will send a request for user accounts, for all the investigators/staff documented on the “Firecrest Site and User Master Spreadsheet”. A Firecrest account must be activated by ICON staff.

Within 24-72 hours after the user account request has been sent to ICON, an email notification will be sent informing the investigator that he/she has been assigned to the study with a link to access the Firecrest portal, a username, and a link to retrieve a password. A How-To User Manual will be available to download. Investigators will automatically be assigned to the GCP and Protocol training once the investigator receives a user account. Investigators will receive weekly training reminders to complete the training.

The GCP and Protocol training modules will be available in the “My Training” tab of the portal. If the training has been previously completed, the status will be listed as completed and the training certification can be downloaded.

8.1.3.1 GCP Training

Each investigator who enrolls a patient is required to complete a GCP training course. GCP training is offered in Firecrest and can be completed when the investigator receives his/her user account login. The GCP training takes approximately 50 minutes to complete

If an investigator has already completed a GCP training course, this certification will also be accepted. It is the responsibility of each investigator to do his/her due diligence by submitting a renewed GCP training certification if the GCP was not completed in Firecrest.

All GCP certifications will be accepted and a copy of the training certificate is to be sent to nrg-gy-gcptraining@nrگونcology.org with the following information:

- Investigator's Name
- Investigator's CTEP ID
- Institution NCI CTEP Code
- Institution Name
- Training Certificate

8.1.3.2 Protocol Training

Each investigator who enrolls a patient is required to complete a protocol-specific training course. The protocol-specific training course is conducted in Firecrest and can be completed when the investigator receives his/her user account login. The protocol-specific training takes approximately 25 minutes to complete.

Upon completion of the protocol-specific training course, please send the investigator's training certificate to the NRG Regulatory Affairs Department by emailing nrg-gy-gcptraining@nrگونcology.org with the following information:

- Study Number
- Investigator's Name
- Investigator's CTEP ID
- Institution NCI CTEP Code
- Institution Name
- Training Certificate

8.2 Patient Entry and Registration (11/07/2016)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < <https://eapps-ctep.nci.nih.gov/iam/index.jsp> >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed on the NRG web menu page by clicking on the OPEN link.

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

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
- The enrolling investigator has completed the GCP and protocol training.

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

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the NRG or CTSU roster.
- To perform registrations you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.

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

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctscontact@westat.com.

9.0 DRUG INFORMATION

9.1 Gemcitabine, Gemzar® (NSC #613327)

9.1.1 Formulation: Gemcitabine HCl is a nucleoside analog that exhibits anti-tumor activity.

9.1.2 Supplier/How Supplied: Gemcitabine HCl is commercially available as a white lyophilized powder in sterile single use vials containing 200mg (10 ml) or 1000 mg (50 ml) of gemcitabine as the hydrochloride salt or as a sterile 38mg/mL sterile solution in sterile single-use vials.

9.1.3 Stability/Storage: Unopened vials of gemcitabine powder are stable until the expiration date indicated on the package when stored at controlled room temperature between 20 to 25°C (68 to 77° F). Unopened vials of gemcitabine injection solution are stable until the expiration date indicated on the package when stored at 2 to 8°C (36 to 46° F). Vials should not be frozen.

9.1.4 Preparation: To reconstitute lyophilized gemcitabine, add 5 ml of 0.9% Sodium Chloride Injection to the 200 mg vials or 25 ml to the 1000 mg vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/ml which includes accounting for the displacement volume of the lyophilized powder. The total volume upon reconstitution will be 5.26 ml or 26.3 ml, respectively. Complete withdrawal of the contents will provide 200 mg or 1 g of gemcitabine, respectively.

The appropriate amount of gemcitabine solution may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/ml. The solution should be clear, colorless to slightly straw colored. Do not administer if discoloration or particulate matter is found. Once the drug has been reconstituted or diluted, it should be stored at controlled room temperature and used within 24 hours.

9.1.5 Administration: The mixed solution will be continuously infused over 30 minutes.

9.1.6 Adverse effects:

*See FDA-approved gemcitabine package insert for a comprehensive list of adverse events associated with gemcitabine.

9.2 Paclitaxel (NSC #673089)

- 9.2.1 **Formulation:** Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi-dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.
- 9.2.2 **Storage:** Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.
- 9.2.3 **Stability:** Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.
- 9.2.4 **Preparation:** Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

All patients should be premedicated with corticosteroids, diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions.

Patients who experience severe hypersensitivity reactions to paclitaxel should not be re-challenged with the drug.

- 9.2.5 Adverse Effects: Consult the package insert for the most current and complete information.

9.3 Carboplatin (Paraplatin® - NSC #241240)

- 9.3.1 Formulation: Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL, or 600mg/60mL of carboplatin.
- 9.3.2 Storage: Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F). Excursions from 15 to 30°C (59 to 86°F) are permitted. Protect from light. Carboplatin multi dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.
- 9.3.3 Preparation: Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C / 77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

See Appendix IV for current dose instructions.

Note; Carboplatin dose will be recalculated if patient has weight change of greater than or equal to 10% from baseline.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must NOT be used for the preparation or administration of carboplatin.

- 9.3.4 Adverse Effects: Consult the package insert for the most current and complete information.
- 9.3.5 Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

9.4 Pegylated Liposomal Doxorubicin (DOXIL®, NSC #712227 Lipodox™; (NSC#673089)

Pegylated liposomal doxorubicin (PLD) is commercially available. All commercially available sources are allowed including:

- * Generic PLD
(<http://www.caraco.com/outserts/Doxorubicin%20HClLip.pdf>)
- * Lipodox ®
(http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203263lbl.pdf)
- * Doxil ® (http://www.doxil.com/assets/DOXIL_PI_Booklet.pdf)

Refer to the PLD package insert ([Doxil](#), [Lipodox](#)[™]) for the most complete and current information on the following:

- 9.4.1 **Formulation:** PLD (doxorubicin HCl liposome injection) is supplied as a sterile, translucent, red liposomal dispersion in 5 mL (Lipodox only), 10 mL, or 30 mL glass, single-use vials. Each vial contains doxorubicin HCl at a concentration of 2 mg/mL.
- 9.4.2 **Storage:** Refrigerate unopened vials of PLD at 2°–8°C (36°–46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on PLD.
- 9.4.3 **Preparation:** PLD doses up to 90 mg must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 mL of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in PLD. Diluted PLD should be refrigerated at 2°C–8°C (36°F–46°F) and administered within 24 hours.

Do not mix with other drugs.

Do not use with any diluent other than 5% Dextrose Injection.

Do not use any bacteriostatic agent, such as benzyl alcohol.

PLD is not a clear solution but a translucent, red liposomal dispersion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

Do not use an in-line filter

- 9.4.4 **Procedure for Proper Handling and Disposal:** Caution should be exercised in the handling and preparation of PLD. The use of gloves is required.

If PLD comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

PLD should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of PLD, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. PLD must not be given by the intramuscular or subcutaneous route.

PLD should be handled and disposed of in a manner consistent with other anticancer drugs.

Adverse Effects: Consult the PLD package insert for the most current and complete information.

Supplier: Commercially available from Ortho Biotech Products, LP Raritan, NJ (DOXIL) and Caraco Pharmaceutical Laboratories Ltd, Detroit, MI (Lipodox).

Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

9.5 Cediranib (AZD2171, NSC 732208)

9.5.1 Chemical Name: 4-[(4-Fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy) quinazoline maleate

9.5.2 Other Names: AZD2171 maleate

9.5.3 CAS Registry Number: 288383-20-0 (for the free base)

9.5.4 Molecular Formula: C₂₅H₂₇FN₄O₃ · C₄H₄O₄

9.5.5 Molecular Weight: 566.59 as maleate salt (450.52 as free base)

9.5.6 Approximate Solubility: The aqueous solubility of AZD2171 is 0.0006 mg/mL for the free base (distilled water, pH 8.1 at 25°C) and 1.9 mg/mL for the maleate salt (distilled water, pH 4.4 at 25°C).

9.5.7 Mode of Action: AZD2171 is a highly potent inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase activity, which inhibits VEGF-dependent angiogenesis, neovascular survival and vascular permeability.

- 9.5.8 How Supplied: Astra-Zeneca supplies and CTEP, NCI, DCTD distributes AZD2171. The agent is available as beige film-coated tablets containing 15 mg, and 20 mg of AZD2171 free base. The 15 mg and 20 mg tablets are 7 mm and 8 mm in diameter, respectively. Each high-density polyethylene bottle contains 35 tablets.

Tablet excipients include mannitol, dibasic calcium phosphate anhydrous, sodium starch glycolate, microcrystalline cellulose, and magnesium stearate with a film coat containing hypromellose 2910, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide.

- 9.5.9 Storage: Store intact bottles at controlled room temperature [20°C-25°C, (68-77°F)] and protect from light and moisture.
- 9.5.10 Stability: Stability studies are ongoing. Dispense AZD2171 tablets in their original containers. Alternatively, if exact quantity is dispensed in a pharmacy bottle, the supply should be assigned a 30-day expiration. If a storage temperature excursion is identified, promptly return cediranib (AZD2171) 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.
- 9.5.11 Route of Administration: Oral. AZD2171 tablets should be taken either one hour before or two hours after meals.
- 9.5.12 Potential Drug Interactions: (11/07/2016)
AZD2171 (cediranib) is primarily metabolized by flavin-containing monooxygenase enzymes (FMO1 and FMO3) and UGT1A4. It is not a substrate of CYP450 enzymes. In vitro studies suggest that AZD2171 (cediranib) is a substrate for P-glycoprotein (Pgp), but not breast cancer resistance protein (BCRP). Since clinically relevant induction or inhibition of FMO enzymes is uncommon, use caution in patients taking concomitant medications that are strong inhibitors (e.g. ketoconazole) or strong inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's Wort) of UGT1A4 or Pgp in particular. If chronic concomitant administration of strong inducers or inhibitors is unavoidable, consult the protocol document and/or the principal investigator before making any dose adjustments.

In vitro studies using hepatic cultures show that cediranib (AZD2171) did not inhibit CYP 1A2, 2A6, 2C8, 2C9, 2C19 and 2E1 and showed no induction of CYP 1A2, 2B6 and 3A4/5. It did weakly inhibit CYP 2D6 and 3A4/5, but this inhibition not expected to cause any clinically

relevant drug interactions. The possibility that cediranib (AZD2171) may induce gastrointestinal CYP3A and UGT enzymes cannot be excluded; therefore the efficacy of hormonal contraceptives may be reduced. Advise women study participants to use an additional non-hormonal contraceptive method.

In vitro studies show that cediranib (AZD2171) is a weak inhibitor of BCRP, Pgp, OATP1B1, OATP1B3, OCT2 and MATE1. Use caution in patients who are taking concomitant medications that are sensitive substrates of these transporters since there is a low potential for drug-drug interactions. *In vivo* studies show that cediranib (AZD2171) could increase exposure of drugs like metformin by inhibiting renal tubular transporter MATE2-K, but this is thought to be infrequent and mild in severity. Cediranib is not an inhibitor of OAT1 or OAT3.

AZD2171 (cediranib) is approximately 95% bound to human plasma proteins, with human serum albumin and α 1-acid glycoprotein accounting for most of this binding. Use caution in patients taking concomitant medications with narrow therapeutic ranges that are also highly protein-bound.

Oral anticoagulants are not absolutely contraindicated during treatment with AZD2171 (cediranib); however, use AZD2171 (cediranib) with caution and increase monitoring in patients while on study. Patients who receive VEGF inhibitors are at increased risk of bleeding and hemorrhage.

- 9.5.13 Patient Care Implications: Agents that inhibit VEGF signaling have the potential to affect wound healing; therefore, it is recommended that AZD2171 is stopped two weeks prior to elective surgery and restarted when the surgical wound has healed. Patients should be excluded from participating in clinical studies with AZD2171 if they have had recent (at least two weeks, or until any wound has completely healed) major thoracic or abdominal surgery prior to study start, or a surgical incision that is not fully healed.

Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for at least 6 weeks after the last dose of cediranib (AZD2171). Refer to the protocol document for specific guidance. **(11/07/2016)**

- 9.5.14 Availability: NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment arm prior to submitting the clinical drug request to PMB. AZD2171 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

AZD2171 is provided to the NCI under a Clinical Trials Agreement (CTA) between AstraZeneca International (the Pharmaceutical Collaborator) and the DCTD, NCI (see Section 12.3).

9.5.15 Agent Ordering and Agent Accountability (11/07/2016)

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.

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.

9.5.16 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 NCI Investigational Agent Oral (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.

9.5.17 Useful Links and Contacts:

- CTEP Forms, Templates, Documents:
<http://ctep.cancer.gov/forms/>

- NCI CTEP Investigator Registration:
PMBRegPend@ctep.nci.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://eapps-ctep.nci.nih.gov/iam/>
 - CTEP Associate Registration and 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)

9.6 Olaparib (AZD2281, NSC 747856)

- 9.6.1 Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one
- 9.6.2 Other Names: AZD2281; KU-0059436; CO-CE 42
- 9.6.3 Classification: PARP inhibitor
- 9.6.4 CAS Registry Number: 763113-22-0
- 9.6.5 Molecular Formula: C₂₄H₂₃FN₄O₃
- 9.6.6 Molecular Weight: 434.46
- 9.6.7 Approximate Solubility: 0.1 mg/mL pH independent solubility across physiologic range
- 9.6.8 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.
- 9.6.9 Description: Crystalline solid
- 9.6.10 How Supplied: AstraZeneca supplies and the CTEP, DCTD distributes olaparib as 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.

- 9.6.11 **Storage:** Store in a secure location below 30° C (86° F). Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.
- 9.6.12 **Stability:** Shelf-life studies are ongoing. If a storage temperature excursion is identified, promptly return olaparib 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 PMBAAfterHours@mail.nih.gov for determination of suitability
- 9.6.13 **Route of Administration:** Tablets can be taken by mouth.
(11/07/2016)
- 9.6.14 **Potential Drug Interactions: (11/07/2016)**
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

- 9.6.15 Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryo fetal survival and development. Therefore, study participants and their partners who are of child-bearing potential should agree to use two (2) highly effective forms of contraception throughout their study participation and for three (3) months after 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

- 9.6.16 Availability: NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment arm prior to submitting the clinical drug request to PMB. Olaparib (AZD2281) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Olaparib (AZD2281) is provided to the NCI under a Clinical Trials Agreement (CTA) between AstraZeneca International (the Pharmaceutical Collaborator) and the DCTD, NCI (see Section 12.3).

- 9.6.17 Agent Ordering and Agent Accountability (11/07/2016)

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.

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.

9.6.18 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 NCI Investigational Agent Oral (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.

9.6.19 Useful Links and Contacts

- CTEP Forms, Templates, Documents:
<http://ctep.cancer.gov/forms/>
- NCI CTEP Investigator Registration:
PMBRegPend@ctep.nci.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://eapps-ctep.nci.nih.gov/iam/>
- CTEP Associate Registration and 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)

9.7 Blood Pressure Cuffs (11/07/2016)

A patient who is randomized to the olaparib and cediranib treatment arm (Arm III) will be given a blood pressure cuff. Blood pressure cuffs that are supplied for this study, are only to be used for this study.

9.7.1 Supply and Distribution: Blood pressure cuffs will be supplied by VWR and distributed by Biologics. Each kit contains a blood pressure monitor (which includes standard size cuff), an adaptor and a large size cuff. Kits will be shipped in the original manufacturer's packaging.

9.7.2 Ordering Instructions: No starter supplies are available. Sites are permitted to order a maximum of 10 Blood Pressure kits at a time for enrolled patients. To obtain the kits, please complete the "Blood Pressure Kit Order Request Form" and fax to Biologics at 919-256-0794. The form is available on the CTSU website. Orders received before 2pm ET, Monday-Friday, will be processed and shipped the same day. Orders received after 2pm ET, will be processed the following business day. All orders will be shipped via FedEx Priority Overnight.

10.0 PATHOLOGY

10.1 Stained Pathology Slide Requirements for Central Review to Confirm Eligibility: Not applicable.

11.0 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

11.1 Reimbursement

See the Funding Sheet found on the CTSU web site (www.ctsu.org).

11.2 Translational Science

Note: Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

11.2.1 Specimen Requirements (11/07/2016)

Specimens listed below should not be submitted until after patient registration and Bank ID assignment.

Sites in **Japan** should refer to Appendix XV for specimen collection and shipping details.

11.2.1.1 Integrated Biomarker Specimen Requirements (11/07/2016) (07/31/2017)

The patient must give permission to participate in this **mandatory** study component.

Participating sites are required to submit the patient's specimens as outlined below.

ALL PATIENTS		
Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens To
CEC Pre-treatment Whole Blood (WB02) ¹	Prior to study treatment	Preclinical Development Research Core (PDRC) <u>the</u>

8mL drawn into CPT (citrate) tube		day the specimen is collected ²
CEC C1D3 Whole Blood (WB03) ¹ 8mL drawn into CPT (citrate) tube	Cycle 1, day 3 of study treatment, only if WB02 was submitted	
BROCA-HR Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to study treatment	NRG BB-Columbus the day the specimen is collected ³
BROCA-HR FFPE Primary Tumor (FP02) ⁴ 2 unstained slides (charged, 10µm) ⁵	Prior to all treatment	NRG BB-Columbus within 2 weeks of registration ³
BROCA-HR FFPE Metastatic Tumor (FM02) ⁴ 2 unstained slides (charged, 10µm) ⁵	<i>Submit one - FP02 is preferred; Submit FM02 only if FP02 is not available</i>	
BROCA-HR FFPE Primary Neoadjuvant Treatment Tumor (FPT02) ⁴ 2 unstained slides (charged, 10µm) ⁵	After patient receives neoadjuvant treatment, only if FFPE tumor is not available from prior to the patient receiving neoadjuvant treatment (i.e., FP02 or FM02).	
BROCA-HR FFPE Metastatic Neoadjuvant Treatment Tumor (FMT02) ⁴ 2 unstained slides (charged, 10µm) ⁵	<i>Submit one – FPT01 is preferred; Submit FMT02 only if FPT02 is not available</i>	
Future Use Whole Blood (WB04) 7-10mL drawn into purple top (EDTA) tube(s) and frozen ⁶	Prior to study treatment	NRG BB-Columbus within 2 weeks of registration ³
Research Pre-treatment Plasma (PB09) prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)	Prior to study treatment	NRG BB-Columbus within 5 weeks of registration ³
Research C2D1 Plasma (PB10) prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)	Cycle 2, day 1, prior to study treatment, only if PB09 was submitted	
Research Final Plasma (PB11) prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)	At disease progression or end of treatment, only if PB09 was submitted	NRG BB-Columbus within 26 weeks of registration ³
ALL PATIENTS RECEIVING OLAPARIB (ARMS II and III)		
Olaparib PK C1D8 Pre-Treatment Plasma (PB01) prepared from 2mL of blood drawn into green top (lithium heparin) tube	Cycle 1, day 8, within 30 minutes prior to administering study drug	NRG BB-Columbus within 2 weeks of registration ³
Olaparib PK C1D8 0.5-1 Hour Plasma (PB02) prepared from 2mL of blood drawn into green top (lithium heparin) tube	Cycle 1, day 8, 0.5-1 hour (+/-5 minutes) after administering study drug	
Olaparib PK C1D8 1-3 Hour Plasma (PB03) prepared from 2mL of blood drawn into green top (lithium heparin) tube	Cycle 1, day 8, 1-3 hours (+/-10 minutes) after administering study drug	
Olaparib PK C1D8 4-6 Hour Plasma (PB04) prepared from 2mL of blood drawn into green top (lithium heparin) tube	Cycle 1, day 8, 4-6 hours (+/-30 minutes) after administering study drug	
ALL PATIENTS RECEIVING CEDIRANIB (ARM III)		
Cediranib PK C1D8 Pre-Treatment Plasma (PB05) prepared from 2mL of blood drawn into purple top (K2EDTA) tube	Cycle 1, day 8, within 30 minutes prior to administering study drug	NRG BB-Columbus within 2 weeks of registration ³

Cediranib PK C1D8 0.5-1 Hour Plasma (PB06) prepared from 2mL of blood drawn into purple top (K2EDTA) tube	Cycle 1, day 8, 0.5-1 hour (+/-5 minutes) after administering study drug	
Cediranib PK C1D8 1-3 Hour Plasma (PB07) prepared from 2mL of blood drawn into purple top (K2EDTA) tube	Cycle 1, day 8, 1-3 hours (+/-10 minutes) after administering study drug	
Cediranib PK C1D8 4-6 Hour Plasma (PB08) prepared from 2mL of blood drawn into purple top (K2EDTA) tube	Cycle 1, day 8, 4-6 hours (+/-30 minutes) after administering study drug	

- CEC whole blood specimens must be shipped the day the specimen is collected. If Cycle 1 Day 3 falls on a Friday or weekend, the C1D3 (WB03) sample may be collected on Cycle 1 Day 4, Day 5, or Day 6. Additionally, patients starting study treatment on a Friday should have their baseline sample (WB02) collected the day prior to starting treatment, if possible. **Please include a note stating if the sample was collected on a day other than the day indicated by the specimen collection time point.**
- Preclinical Development Research Core, NCI, NIH, Bldg. 10, Rm 12N218, 10 Center Dr, Bethesda, MD 20892, Phone: 301-496-1547, Emails: trepel@helix.nih.gov, leesun@mail.nih.gov, leemin@mail.nih.gov, akira.vuno@nih.gov; **Note: Please notify the PDRC (via the four email addresses provided) when a patient is scheduled for a blood draw and when the specimen will be shipped. The FedEx tracking number should be included in the shipment. Additionally, CEC whole blood specimens must be shipped the day the specimen is collected. If the specimen absolutely cannot be shipped the same day, a note detailing why the specimen needed to be shipped the next day must be included. If the specimen cannot be shipped within 24 hours, it should be discarded.**
- NRG BB-Columbus / Protocol NRG GY004, Nationwide Children’s Hospital, 700 Children’s Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org.
- A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the NRG BB-Columbus.
- If patient consents to the optional FFPE collection (specimen codes ending in “01”; section 11.2.1.2) and a block will be submitted on a permanent basis to fulfill both the mandatory (specimen codes ending in “02”; section 11.2.1.1) and optional (specimen codes ending in “01”; section 11.2.1.2) specimen requirements, then label the block with the specimen code ending in “01.” Complete and ship both the “01” and “02” specimen transmittal forms (i.e., Form TR) with the block.**
- Do not use glass blood collection tubes.

11.2.1.2 Exploratory Biomarker Specimen Requirements (11/07/2016) (07/31/2017)

If the patient gives permission to participate in this **optional** study component, then participating sites are required to submit the patient’s specimens as outlined below.

ALL PATIENTS		
Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens To
FFPE Primary Tumor (FP01)* 1st Choice: block ¹ 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to all treatment (<i>Preferred FFPE</i>)	NRG BB-Columbus within 8 weeks of registration ²
FFPE Metastatic Tumor (FM01)* 1st Choice: block ¹ 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to all treatment (<i>Optional if FP01, FRP01, FRM01, FPT01, or FMT01 is submitted</i>)	
FFPE Recurrent Primary Tumor (FRP01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment (<i>Optional if FP01, FM01, FRM01, FPT01, or FMT01 is submitted</i>)	
FFPE Recurrent Metastatic Tumor (FRM01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment (<i>Optional if FP01, FM01, FRP01, FPT01, or FMT01 is submitted</i>)	

<p>FFPE Primary Neoadjuvant Treatment Tumor (FPT01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)</p>	<p>After patient receives neoadjuvant treatment, only if FFPE tumor is not available from prior to the patient receiving neoadjuvant treatment (i.e., FP02 or FM01). (Optional if <i>FP01, FM01, FRP01, FRM01, or FMT01</i> is submitted)</p>	
<p>FFPE Metastatic Neoadjuvant Treatment Metastatic Tumor (FMT01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)</p>	<p>After patient received neoadjuvant treatment, only if FFPE tumor is not available from prior to the patient receiving neoadjuvant treatment (i.e., FP02 or FM01). (Optional if <i>FP01, FM01, FRP01, FRM01, or FPT01</i> is submitted)</p>	

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to NRG BB-Columbus.

1 If patient consents to the optional FFPE collection (specimen codes ending in “01”; section 11.2.1.2) and a **block** will be submitted on a permanent basis to fulfill both the mandatory (specimen codes ending in “02”; section 11.2.1.1) and optional (specimen codes ending in “01”; section 11.2.1.2) specimen requirements, then label the **block** with the specimen code ending in “01.” Complete and ship both the “01” **and** “02” specimen transmittal forms (i.e., Form TR) with the **block**.

2 NRG BB-Columbus / Protocol NRG GY004, Nationwide Children’s Hospital, 700 Children’s Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org.

11.2.2 Specimen Procedures (11/07/2016)

A detailed description of specimen procedures can be found in Appendix V.

A detailed description of specimen procedures for sites in **Japan** can be found in Appendix XV.

11.2.3 Laboratory Testing

Assay details are included in Appendix VI.

11.2.3.1 Circulating Endothelial Cells (Integrated Biomarker) (11/07/2016)

Whole blood collected pre-treatment and on cycle 1, day 3, will be **shipped by sites directly** to the Preclinical Development Research Core (PDRC) on the day the specimen is collected for analysis of circulating endothelial cells (CECs) by flow cytometry.

Preclinical Development Research Core

NCI, NIH

Bldg. 10, Rm 12N218

10 Center Dr, Bethesda, MD 20892

Phone: 301-496-1547

Emails: trepel@helix.nih.gov, leesun@mail.nih.gov, leemin@mail.nih.gov, akira.yuno@nih.gov

11.2.3.2 BROCA-HR (Integrated Biomarker) (11/07/2016)

DNA extracted from whole blood and two unstained sections (charged, 10µm) of formalin-fixed, paraffin-embedded (FFPE) primary or metastatic tumor will be **shipped every six weeks by the NRG BB-Columbus** to Dr. Elizabeth Swisher for BROCA-HR testing.

Swisher Lab

ATTN: Kathy Agnew
University of Washington
1959 NE Pacific St
HSB BB632
Seattle, WA 98195
Phone: 206-685-7927
Emails: kagnew@uw.edu, ovcalab@uw.edu

Special Note Regarding Genetic Testing: Given the potential clinical implications conferred by detecting a germline mutation in one of these proven cancer genes, the following disclosure procedure articulated by the American College of Medical Genetics and Genomics will be followed.

1. For each subject with a clinically actionable result from BROCA sequencing, the testing laboratory will contact the NRG study PI at the enrolling institution to notify them that a research test result of potential clinical importance has been identified in one of their study participants. Please include the mutation in the genetic counselor's report and place a copy of the report in the research record.
2. The PI at the enrolling institution will be responsible for contacting the study participant to inform them that study-related research has uncovered genetic information that might affect their clinical care. Each participant can then:
 - a. Elect not to receive the information, which will be retained by the enrolling physician in the event that the participant changes their mind at a later date.
 - b. Elect to receive the information, in which case pre-test counseling should be provided prior to clinical testing of a freshly-drawn blood sample. After being counseled, the patient may (i) decide not to undergo clinical testing for the mutation identified under research, or (ii) decide to undergo clinical testing, in which case a new blood sample will be collected at the enrolling site and shipped directly to the CLIA-approved laboratory for mutation confirmation at no cost to the patient. The clinical genetic test result will be returned to the clinicians involved in counseling and managing this aspect of the patient's care and it will be their responsibility to disclose the results to the patient.

11.2.3.3 Future Olaparib Assay Development (Integrated Biomarker)

Frozen whole blood will be **batch shipped by the NRG BB-Columbus** to Myriad for development of an olaparib companion diagnostic test.

11.2.3.4 Plasma Angiome (Integrated Biomarker)

Aliquots (1.5mL) of frozen plasma will be **batch shipped by the NRG BB-Columbus** upon trial completion to Duke University for analysis of the plasma angiome.

Andrew Nixon
Phase I Biomarker Laboratory
Duke University Medical Center
395 MSRB Building
Research Dr.

Durham, NC 27710
Phone: 919-613-7883
FAX: 919-668-3925
Email: anixon@duke.edu

11.2.3.5 Olaparib and Cediranib PK (Integrated Biomarker)

Frozen plasma will be **batch shipped by the NRG BB-Columbus** every six months to Covance for olaparib and cediranib PK.

11.2.3.6 BRCA1 Promoter Methylation (Exploratory Biomarker)

Five unstained sections (charged, 5µm) and one H&E stained section will be **batch shipped by the NRG BB-Columbus** upon trial completion to Dr. Douglas Levine for analysis of BRCA1 promoter methylation.

Dr. Douglas Levine
ATTN: Narciso Olvera
GYN Research Lab, Z-427G
Memorial Sloan Kettering Cancer Center
417 E 68th St
New York, NY 10065
Phone: 646-888-3208
Email: gynreslab@mskcc.org

11.2.3.7 BRCA1 Immunohistochemistry (Exploratory Biomarker)

Three unstained sections (charged, 5µm) and one H&E stained section will be **batch shipped by the NRG BB-Columbus** upon trial completion to Dr. Douglas Levine (address above) for BRCA1 immunohistochemistry.

11.3 Quality of Life / Patient-Reported Outcomes (11/07/2016)

The PRO endpoints proposed for this trial represent the best available approach to measuring disease related symptoms-physical (DRS-P) and treatment side effects (TSE) that are most important to women with advanced ovarian cancer. The 9-item NFOSI-18 DRS-P is the main PRO endpoint for the trial and has a pre-specified analysis plan. All other endpoints (TSE, F/WB, Ntx-4 and EQ-5D) are secondary and will be analyzed as exploratory objectives (see Appendix X).

The following PRO assessments will be performed every 12 weeks for 3 years, unless the patient withdraws from study participation. PRO assessments should continue post-progression.

1. (primary QOL/PRO endpoint): PRO: NFOSI-18 DRS-P
2. (secondary): PRO: NFOSI-18 TSE
3. (secondary): PRO: NFOSI-18 F/WB
4. (secondary): PRO: NTX-4
5. (secondary): EQ5D

Instructions for completing Quality of Life scantron form

Whenever possible, the QOL survey should be administered at the clinic visit before the patient is seen by the physician, before evaluations are performed, and before test results are shared with her. In the event the questionnaires are not administered at the clinic visit, the QOL data can be collected by telephone or mail as back-up methods, with telephone data collection being the preferred back-up method

Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to the cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing the patient's response.

Review the questionnaire for completeness before the patient leaves. If the patient marked more than one answer per question, ask the patient which answer best reflects how she is feeling. If the patient skipped a question or questions, assure the she noted in the space provided that she has chosen not to answer those questions.

12.0 DATA AND RECORDS

Data Management/Collection

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 Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Each person responsible for data entry must be on the NRG roster in order to receive access to Medidata 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 (iMedidata-Notification@mdsol.com) to activate their account. 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. Once an account is activated, eLearning modules will be available for Rave RDC instructions. 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 listed 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 website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctscontact@westat.com.

NRG Data Management Forms (11/07/2016) (07/31/2017)

The following forms must be completed for all patients registered and submitted to the NRG Statistical and Data Management Center (SDMC) according to the schedule below. NRG electronic case report forms must be submitted through the Medidata Rave Electronic Data Entry System. All amendments to forms submitted through Medidata Rave must also be submitted through Medidata Rave. The operative report, discharge summary, pathology reports, and patient questionnaires can be sent to the NRG Statistical and Data Management Center via postal mail or uploaded in Medidata Rave. The upload option is an alternative method to submitting paper reports.

This study will be monitored by the **Abbreviated** Clinical Data System (CDUS) Version 3.0 CDUS data will be submitted quarterly by the January 31, April 30, July 31 and October 31 due dates to CTEP by electronic means.

Form	Comments
Baseline Folder <i>(forms due within 2 weeks of registration)</i>	
Baseline/History Forms: <ul style="list-style-type: none"> - Visit Information- Baseline Form - Registration Form - Pre-Treatment Summary Form - Pre-Study History Information Form - On Study History Surgery Form - Pre-Study History Chemotherapy Information Form - Pre-Study Radiation Therapy Information Form - Specimen Consent - ECHO/MUGA Form - ECG Information Form - Concomitant Medications Form - Vitals Form - Bio-Marker Information Form - Medical History Form - BRCA Status Form 	The appropriate forms will load in baseline folder based on answers reported on the corresponding Baseline Visit Information form.
Visit Folder <i>(forms due with in 2 weeks of completion of each cycle)</i>	
Cycle Information and Treatment Forms:	

<ul style="list-style-type: none"> - Visit Information Form - Lab Loader - Cycle Drug Information Form - Labs and Chemistries Form - Vitals Form - ECHO/MUGA Form - ECG Information Form - Concomitant Medications Form - Bio-Marker Information Form <p>Toxicity form:</p> <ul style="list-style-type: none"> - Section 1 form - Adverse Event Form - Adverse Event Grades 	<p>The appropriate forms will load in folder based on answers reported on the corresponding Visit Information form.</p>
<p>Solid Tumor Evaluation Folder <i>(Forms due within 2 weeks of disease evaluation)</i></p>	
<p>Solid Tumor Evaluation Forms:</p> <ul style="list-style-type: none"> - Target Lesions Form - No Target Lesions Form - Non-Target Lesions Form - New Target Lesions Form - Status and Response Form 	
<p>PRO</p>	
<p>Patient-reported outcomes should be performed every 12 weeks for 3 years, unless the patient withdraws from study participation. Patients who stop study treatment for any reason other than death or refusal should be assessed on schedule. PRO assessments should continue post-progression.</p>	<p>Scantrons can be ordered by going to the NRG-GY004 protocol documents on the CTSU Website and downloading the SCANTRON ORDER FORM to your computer. Please complete the form electronically and email form to nrg-gy-scantronorders@nrgoncology.org or fax to 716-845-8854. For questions, please contact NRG at 716-845-5702</p> <p>Completed Scantrons should be mailed via postal mail to the address below</p> <p style="text-align: center;">NRG Oncology SDMC Roswell Park Cancer Institute Elm & Carlton Streets Buffalo, NY 14263-0001 Phone: 716-845-5702</p>
<p>Translational Research Folder</p>	
<p>TR Forms:</p> <ul style="list-style-type: none"> - CEC Pre-treatment Whole Blood (WB02) - CEC C1D3 Whole Blood (WB03) - BROCA-HR Whole Blood (WB01) - BROCA-HR FFPE Primary Tumor (FP02) <i>FP02 or FM02 must be submitted*</i> - BROCA-HR FFPE Metastatic Tumor (FM02) <i>FP02 or FM02 must be submitted*</i> 	<p>The appropriate forms will load in the Translational Research Folder based on the answers reported on the Specimen Consent form.</p> <p>An electronically completed copy of Form TR must accompany each specimen shipped. Handwritten forms will not be accepted.</p>

<ul style="list-style-type: none"> - BROCA-HR FFPE Primary Neoadjuvant Treatment Tumor (FPT02) <i>FPT02 or FMT02 should only be submitted if FP02 or FM02 are not available*</i> - BROCA-HR FFPE Metastatic Neoadjuvant Treatment Tumor (FMT02) <i>FPT02 or FMT02 should only be submitted if FP02 or FM02 are not available*</i> - Future Use Whole Blood (WB04) - PK Olaparib C1D8 Pre-Treatment Plasma (PB01) - PK Olaparib C1D8 0.5-1 Hour Plasma (PB02) - PK Olaparib C1D8 1-3 Hour Plasma (PB03) - PK Olaparib C1D8 4-6 Hour Plasma (PB04) - PK Cediranib C1D8 Pre-Treatment Plasma (PB05) - PK Cediranib C1D8 0.5-1 Hour Plasma (PB06) - PK Cediranib C1D8 1-3 Hour Plasma (PB07) - PK Cediranib C1D8 4-6 Hour Plasma (PB08) - FFPE Primary Tumor (FP01) - FFPE Metastatic Tumor (FM01) <i>optional</i> - FFPE Recurrent Primary Tumor (FRP01) <i>optional</i> - FFPE Recurrent Metastatic Tumor (FRM01) <i>optional</i> - Research Pre-treatment Plasma (PB09) - Research C2D1 Plasma (PB10) - Research Final Plasma (PB11) 	<p>WB01-WB03 are due 1 week from registration.</p> <p>FP02 and FM02 are due 2 weeks from registration. *If patient consents to the optional FFPE collection (specimen codes ending in “01”; section 11.2.1.2) and a <u>block</u> will be submitted on a permanent basis to fulfill both the mandatory (specimen codes ending in “02”; section 11.2.1.1) and optional (specimen codes ending in “01”; section 11.2.1.2) specimen requirements, then label the <u>block</u> with the specimen code ending in “01.” Complete and ship both the “01” <u>and</u> “02” specimen transmittal forms (i.e., Form TR) with the <u>block</u>. Complete and ship both the “01” <u>and</u> “02” specimen transmittal forms (i.e., Form TR) with the <u>block</u>. Complete the “01” Form TR as “collected” and include all requested specimen information. Complete the “02” Form TR as “not collected” and specify “submitted for another study.”</p> <p>WB04 and PB01-PB08 are due 2 weeks from registration.</p> <p>FP01, FM01, FRP01, and FRM01 are due 8 weeks from registration.</p> <p>PB09-PB11 are due 5 weeks from registration.</p>
<p>Treatment Completion Folder <i>(forms due within 2 weeks of Treatment Completion)</i></p>	
<p>-Treatment completion form</p>	
<p>Follow-up Visit Folder <i>(Forms due within 2 weeks of follow-up visits, disease progression or death)</i></p>	
<p>Visit Information Follow-Up Form Lab Loader Follow- up form Non-Protocol Therapy Form Concomitant Medications Form Labs and Chemistries Form Bio-Marker Reporting Form</p> <p>Follow-Up Period Adverse event:</p> <ul style="list-style-type: none"> - Part 1Form - Adverse Event Form - AE Grades Form 	<p>The appropriate forms will load in folder based on answers reported on the corresponding Visit Information form.</p>

- The required source documents, per appendix XII of the protocol, will be uploaded via Medidata Rave in the appropriate Form Folders

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This study is a three-arm, randomized phase III clinical trial. The treatment for each enrolled patients will be randomized, and consist of either:

- a. Carboplatin with paclitaxel or gemcitabine or PLD (reference regimens)
- b. Olaparib (E1)
- c. Olaparib + cediranib (E2).

The overall objective of this study is to evaluate the relative efficacy and safety of these treatment regimens in patients with recurrent high-grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer.

13.2 Treatment allocation

Treatments will be sequentially allocated from lists consisting of randomly permuted study treatments within blocks. This allocation procedure tends to allocate each of the study regimens to an equal number of enrollees within the 8 groups defined by combinations of the following factors:

- a. Germline BRCA1/2 mutation status (Yes vs No)
- b. Prior platinum-free interval (6-12 months vs >12 months).
- c. Prior angiogenic treatment for ovarian cancer (Yes vs No).

Patients are enrolled onto the study via a web-based registration system. The randomized treatment for each individual remains concealed until after the registration process has been completed.

13.3 Measures of Efficacy and Safety

The principal observations for evaluating the therapeutic efficacy and safety of the study regimens are:

- a. Primary efficacy endpoint: Progression-free survival (PFS) by RECIST 1.1 as determined by the treating physician.
- b. Secondary efficacy endpoint: Overall survival (OS) and response.
- c. Safety endpoints: frequency and severity of adverse effects as defined by Common Terminology Criteria for Adverse Events (CTCAE).
- d. Patient reported outcomes as measured by the NFOSI-18, DRS-P.
- e. Time from randomization to the first non-study, anti-cancer treatment or death.
- f. Time from randomization to the second non-study, anti-cancer treatment or death.

13.4 Progression-Free and Overall Survival

The onset of progression will be determined using RECIST 1.1 criteria (see Section 15). For analyses of the primary endpoint, the PFS duration will be defined as the time between the date of enrollment (and randomization) onto the study to the date of disease progression or death. The date of progression will be determined by the local clinical staff. The following censoring will apply to the primary PFS analyses:

1. Patients with no baseline tumor assessments will be censored on the date of randomization
2. Patients with no adequate post baseline tumor assessments and no death reported within 2 scan intervals following randomization will be censored on the date of randomization.
3. Patients who have not progressed and are alive will be censored on the date of the last tumor assessment without documented disease progression
4. Patients who have disease progression or death immediately after 2 or more consecutive missing tumor assessments will be censored at the date of last tumor assessment prior to the missing tumor assessments

In the sensitivity analyses (section 13.9), patients who switch to a non-protocol anticancer treatment prior to disease progression or discontinuing study treatment will be censored on the date of the last tumor assessment preceding the start of the non-protocol therapy.

Tumor assessments will be time-based at 9 +/- 1 weeks for the first year and 12 +/- weeks thereafter throughout the study. For the purposes of the primary analyses, the duration of PFS will be determined by the treating physician.

Independent Radiologic Review

The radiographic images will be prospectively collected and stored centrally for a blinded, independent central review (BICR) using RECIST 1.1 (as is done for the local evaluation). The details for storing and reviewing images will be available in separate documents. Sensitivity analyses using the BICR are described below in Section 13.9.2. Results from the BICR will not be communicated to investigators, and the management of patients will be based solely upon the results of the RECIST assessment conducted locally, at the institution.

Expected Median Duration of Progression-Free and Overall Survival

The expected median durations of progression-free and overall survival for ovarian cancer patients with high-grade serous or endometrioid recurrent platinum-sensitive disease treated with standard platinum-based treatment are 12 months and 38 months, respectively.

13.5 Enrollment (07/31/2017)

The target enrollment for this study was originally 450 eligible patients but due to faster than expected accrual and in order to allow greater participation from international sites (which are not fully involved yet), the target has been raised to 549 patients. This will have the additional benefit of moving up the projected final analysis date by approximately 5 months. However, this change leaves the statistical analysis plan completely untouched.

GOG-0213 is a recently completed trial that targeted ovarian cancer patients with platinum sensitive disease. The accrual rate that study was 238 patients per year. Approximately 76% of those patients had a high grade serous or endometrioid cancer. Therefore, for planning purposes, it was estimated that approximately 180 eligible patients per year (15 patients per month) would be available for the current study and therefore, the enrollment period would require at least 2.5 years. However, after two months of ramp up, accrual averaged 15 patients for 4 months and then has averaged ~30 patients per month for the next 8 months. At this rate of accrual, we project the accrual of 549 patients to take approximately 20-24 months. It is anticipated that 30% (135) of these women will have at least one deleterious germline BRCA1 or BRCA2 mutation.

13.6 Study Hypotheses

13.6.1 Null Hypotheses for Primary Endpoint (PFS):

1. $H_{C:E1,pfs}^{\dagger}$: Olaparib (single agent) does not extend the duration of PFS compared to chemotherapy in patients with recurrent high-grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer.
2. $H_{C:E2,pfs}$: Olaparib and cediranib does not extend the duration of PFS compared to chemotherapy in patients with recurrent high-grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer.
3. $H_{E1:E2,pfs}$: Olaparib and cediranib does not extend the duration of PFS compared to olaparib (single agent) in patients with recurrent high-grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer.

† Each hypothesis has two subscripts. The first is the treatment comparison. C=reference treatment group (chemotherapy). E1=Olaparib treatment group (experimental group 1). E2=Olaparib+Cedirinib treatment group (experimental group 2). The second subscript is the outcome measure: PFS=Progression-free survival.

13.7 Type I Error Allocation

This study will use a hierarchical testing procedure for testing $H_{C:E1,PFS}$, $H_{C:E2,PFS}$ and $H_{E1:E2,PFS}$. First, the PFS times for the group of individuals who were randomized to the Olaparib+Cedirinib combination will be compared to the group randomized to chemotherapy ($H_{C:E2,pfs}$). If this null hypothesis is not rejected, then $H_{C:E1,pfs}$ and $H_{E1:E2,pfs}$ will not be evaluated. If the null hypothesis, $H_{C:E2,pfs}$, is rejected, then the PFS for those individuals who were randomized to Olaparib-alone will be compared to the group randomized to chemotherapy ($H_{C:E1,pfs}$). Finally if both null hypotheses, $H_{C:E2,pfs}$ and $H_{C:E1,pfs}$, are rejected, then the PFS for the groups randomized to each of the experimental regimens ($H_{E1:E2,pfs}$) will be compared. The type I error for each of these hypothesis tests will be 0.025 for a one-tail test.

13.8 Statistical Power for $H_{C:E2,pfs}$ $H_{C:E1,pfs}$ $H_{E1:E2,pfs}$

Starting in September 2017, some control arm patients began taking non-protocol maintenance therapy prior to documentation of disease progression, in the context of FDA approvals of new drugs in the maintenance setting. These protocol violations tend to reduce the power of the study. In response to this, the design is being amended to increase the number of PFS events required for the primary analysis to 265 (from 204) to compensate for the loss of power. The timing of the interim analysis is modified accordingly.

(Lachin,1986) approximates the control group hazard rate, adjusted for noncompliance, as the average of the hazards in the control and experimental arms weighted by the noncompliance rate among the controls. Specifically, the adjusted hazard in the controls is estimated as

$$\lambda'_C = (1 - \omega_C)\lambda_C + \omega_C\lambda_E$$

where ω_C is the proportion of control patients who are noncompliant, and (λ_C, λ_E) are the hazards in the control and experimental arms respectively, when patients are fully compliant with the treatment plan. From this, the adjusted hazard ratio is approximated by

$$HR' = [(1 - \omega_C)HR^{-1} + \omega_C]^{-1}$$

This approximation assumes that the hazard for the experimental arm (λ_E) applies to control patients who initiate parp inhibitor maintenance therapy before documentation of disease progression. Table 13.8 shows how the noncompliance rate in the control arm impacts the hazard ratio estimate for the experimental arms (reference: controls) and the loss of power, given 265 events are available at the final analysis. The assumptions in the Lachin(1986) methods are conservative when applied to this study, tending to over-correct for the effect of noncompliance among the controls. For a given noncompliance rate, the adjusted hazard ratio and power estimates can be considered worst-case scenarios.

Table 13.8: The relationship between noncompliance, hazard ratio, and power

Noncompliance in the Control Arm	Adjusted HR	Power for 265 events
0	0.6500	0.935
0.20	0.6989	0.812
0.22	0.7042	0.794
0.24	0.7096	0.773
0.26	0.7151	0.750
0.28	0.7206	0.727
0.30	0.7263	0.702

The study will be considered sufficiently mature for the final analyses of $H_{C:E2,PFS}$ and $H_{C:E1,PFS}$ when there are at least 265 PFS events among those individuals randomized to either the chemotherapy regimen or the combination regimen (E2).

This sample size provide 80% power for detecting a true treatment PFS hazard ratio of 0.70 for the hypotheses $H_{C:E2,PFS}$. If the null hypothesis, $H_{C:E2,PFS}$, is rejected and there are at least 265 PFS events at this time among those randomized to the chemotherapy regimen or the single-agent olaparib regimen then the null hypothesis, $H_{C:E1,PFS}$, will then be evaluated. The power for $H_{C:E1,PFS}$ will be at least at least 80%. Assuming a constant failure rate, a 0.70 hazard ratio is comparable to increasing the expected median time to first progression or death from 12 months to 17.1 months. The study will be considered sufficiently mature to assess $H_{E1:E2,PFS}$ when there are at least 204 PFS events among those individuals randomized to either the Olaparib or the Olaparib+Cediranib regimens. This sample size provides 85% power for a 0.65 hazard ratio. The comparison between the experimental arms is not impacted by noncompliance in the control arm.

Twenty four months after enrolling the last patient (excluding Japan Phase I patients), follow-up for the primary endpoint may be suspended. Simulations suggest that 230 PFS events can be expected at this time, and the analysis would have 80% power to detect a diluted hazard ratio of 0.691. A control arm noncompliance rate of 22% implies a true treatment hazard ratio of 0.636. The decision to suspend will be informed by the number of patients at risk, the effect of control group consent withdrawal on the at-risk set, and the time to obtaining 265 PFS events. (8/15/2019)

13.9 Analytic Procedures for Testing Hypotheses: $H_{C:E2,PFS}$ $H_{C:E1,PFS}$ $H_{E1:E2,PFS}$

13.9.1 Primary Analysis

A log rank procedure will be used to evaluate each of the study hypotheses. The log rank procedure will be stratified by germline BRCA1/2 mutation status (yes vs no), last platinum-free interval (6-12 months, vs > 12 months) and prior antiangiogenic treatment (yes vs no). The analysis of PFS will consider all deaths as events, regardless of the cause of death.

For the primary analyses patients will be grouped according to their randomly assigned treatment. Patients will be included in the analysis regardless of their compliance with their assigned treatment plan. The primary analyses will use the duration of PFS as it is determined by the clinical investigator responsible for treating the patient.

Inferences regarding the significance of hypothesis tests will be made based on the above log rank tests; however, similarly structured proportional hazards models will also be run for the presentation of hazard ratios (HRs) and corresponding confidence intervals (CIs).

13.9.2 Sensitivity Analyses

The following sensitivity analyses for PFS will be done to address the potential stated biases.

Evaluation-time bias

An interval-censored log-rank test (as implemented in SAS[®] Proc ICLIFETEST) will be used, which will otherwise be as described above in section 13.9.1.

Attrition-time bias

In addition to the censoring rules in Section 13.4, patients who receive non-protocol anticancer therapy prior to disease progression will be censored at the time of their last disease assessment prior to the start of non-protocol therapy. The primary log-rank test from section 13.9.1 will be used. Additionally a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary PFS

analysis is reversed will provide an assessment of the independent censoring assumption.

Assessment Bias

As described above in section 13.4, a BICR will be done for all scans. A proportional hazards regression model (using the stratification factors and ITT approach specified for the log-rank tests in section 13.4) will be done using the BICR-assessed PFS. If there is an important discrepancy between the primary analysis using investigator assessments and this sensitivity analysis using BICR assessments, then the proportion of subjects with central but no site confirmation of progression will be summarized. The approach of imputing an event at the next visit in the investigator assessed analysis may help inform the most likely HR value, but only if an important discrepancy exists.

As suggested by Amit, et al (2011), disagreements between the local and BICR assessments of RECIST progression will be summarized with the following by treatment arm:

- the early discrepancy rate (EDR), which is the frequency of local progressions declared early compared to the BICR (≥ 2 weeks earlier) and including progressions declared locally but not by BICR as a proportion of all local progressions, and
- the late discrepancy rate (LDR) which is the frequency of local progressions declared later than BICR progressions (≥ 2 weeks later) and including progressions declared by BICR but not locally as a proportion of all discrepancies (including early and late discrepancies).

Differential concordance for each measure will be calculated as the EDR (or LDR) value for each experimental arm minus the value for the control arm. Negative differential concordance for EDR or positive differential concordance for LDR would be indicative of bias in the local PFS assessment in favor of an experimental arm.

13.10 Interim Analyses (07/31/2017)

Interim and final reports will include an accounting of all patients registered onto the study, regardless of their eligibility status or compliance to their assigned treatment.

An interim analysis will be performed when at least $265/2=133$ PFS events (approximately 50% of the information time) have been observed among those women who were randomly assigned to either the reference regimen or the Olaparib+Cediranib regimen. Assuming that the accrual is as projected then this interim analysis is expected to occur approximately 2.0 years after initiating accrual, depending on the actual accrual rate.

The interim analysis will include an assessment of futility. An O'Brien and Fleming-like (OBF-like) boundary ($\beta(t)=2-2\Phi(Z_{\beta/2}/\sqrt{t})$, Kim, 1987) for type II error will be calculated at the time of the interim analysis. Calculation of these boundaries requires that the fraction of the total information at the interim analysis be specified. The fraction of information will be determined as the observed number of PFS events among those who are included in the $H_{C:E2,PFS}$ hypothesis test divided by the targeted number of PFS required for the final analysis of this hypothesis. If $H_{C:E2,PFS}$ is not deemed futile, then the futility of $H_{C:E1,PFS}$ will also be assessed at this time using the same type II error spending function, but the boundary for its futility will depend on the number of PFS events among the individuals involved in that comparison. It is worth emphasizing that if the interim analysis of $H_{C:E2,PFS}$ indicates futility then the hierarchical testing procedure also makes $H_{C:E1,PFS}$ and $H_{E1:E2,PFS}$ futile.

While the precise boundaries will be calculated at the time of the interim analysis, the OBF-like boundary evaluated at 50% information time is approximately comparable to requiring that the observed PFS hazard for the experimental regimens to be at least 8% lower than the observed PFS hazard of the chemotherapy group. Otherwise, consideration will be given to stopping the enrollment onto that experimental regimen and concluding that it is unlikely that the experimental regimen prolongs PFS relative to chemotherapy. If the DMC decides to stop enrollment onto both experimental regimens then the study will be closed to accrual.

At the time of the final PFS analysis, an interim analysis for OS will be performed. We anticipate that approximately 25% of the 265 required OS events will have occurred at the time of the final PFS analysis. The same order of testing hypotheses that will be used for the final OS analysis will be used for the interim OS analysis. Statistical significance will be declared at the interim analysis for OS if the null hypothesis for PFS is rejected and the observed p-value for OS is $p < 0.0001$. This allows the significance level at the final analysis for OS to be controlled at the 2.5% level (1-sided) (Haybittle J L 1971).

The NRG Data Monitoring Committee (DMC) meets at least semi-annually. The dates for these meetings are administratively scheduled without any specific knowledge of the study results. Approximately eight weeks prior to these meetings, the database is locked in order to prepare a progress report. If the prerequisite number of events has been attained, an interim analysis is also prepared and presented to the DMC at their meeting. The decision to terminate accrual to a particular treatment or the entire study or to release study results includes consideration of toxicities, treatment compliance, overall survival as well as results from external studies.

13.11 Overall Survival and Clinical Response

The expected median overall survival in this study population is about 38 months. A final analysis of overall survival will be conducted when there are at least 265 deaths among those individuals randomized to either the chemotherapy regimen or the combination regimen (E2). A log rank test stratified by germline BRCA1/2 mutation status (yes vs no), last platinum-free interval (6-12 months, vs > 12 months) and prior antiangiogenic treatment (yes vs no). will be used to compare the distributions of survival times between treatment groups. The type I error for this test will be set to 0.025 (one-tail) and this null hypothesis ($H_{C:E2,OS}$) will not be rejected unless the hypothesis regarding PFS ($H_{C:E2,PFS}$) was previously rejected. If $H_{C:E2,PFS}$ is rejected, then this sample size provides 80% power if the combination of olaparib and cediranib reduces the death rate 30% ($HR=0.70$) relative to standard platinum-based chemotherapy. Assuming a constant hazard, a hazard ratio of 0.70 is comparable to increasing the median duration of survival approximately 20 months. Similarly, the rejection of $H_{C:E1,OS}$ and $H_{E1:E2,OS}$ will require first rejecting $H_{C:E1,PFS}$ and $H_{E1:E2,PFS}$, respectively.

Assuming that 80% of the patients enrolled onto this study have at least one target lesion, the standard error of the difference between two treatment groups in the proportion responding is limited to 6.4%.

13.12 Patient-Reported Outcomes

The analyses of PROs described here are not intended to be used for regulatory drug approval. These analyses are for research purposes. The primary objective of this component of the study is to assess patient-reported scores of disease-related symptoms among the study treatments. The primary measure for disease-related symptoms is the NFOSI-DRS-P, which is a 9-item PRO (a subset of items from the NFOSI-18). The NFOSI-DRS-P score for the i^{th} patient-assessment is calculated as

$$S_i = M * \frac{\sum_{j=1}^J (\delta_{ij} * s_{ij})}{\sum_{j=1}^J \delta_{ij}}$$

where δ_{ij} is equal to 1 when the j^{th} item has a valid response, otherwise it is equal to 0, s_{ij} is the response score of the j^{th} item and M is the number of items in the subscale. The response score for each item ranges from 0 to 4, where higher values indicate preferred states. The NFOSI-DRS-P score for a particular patient-assessment time is considered valid if the patient provides valid responses to at least 5 of the score's items, otherwise it is considered incomplete and, for the purposes of analyses, it is treated as if it is missing.

1. **$H_{C:E1,DRS}$** : Olaparib (single agent) does not alter NFOSI-DRS-P scores compared to chemotherapy in patients with recurrent high-grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer.

2. **H_{C:E2,DRS}** : Olaparib and cediranib does not alter NFOSI-DRS-P scores compared to chemotherapy in patients with recurrent high-grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer.
3. **H_{E1:E2,DRS}**: Olaparib and cediranib does alter DRS-P scores compared to olaparib (single agent) in patients with recurrent high-grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer.

A mixed-effects model will be used to estimate and compare the mean NFOSI-DRS-P scores for the treatment groups. Model covariates will include the patients' randomly assigned study treatment, age at enrollment onto the study, initial performance status, pre-treatment NFOSI-DRS-P score, and assessment time. The primary analyses will include all patients enrolled onto the study regardless of their compliance with the study treatment or eligibility status, grouped by their randomly assigned study treatment. Individuals will need to provide at least one baseline (pre-treatment) and one follow-up PRO assessment to be included in the mixed model analyses.

A mixed model will be used to conduct a test of $H_{C:E1,DRS}$ and $H_{C:E2,DRS}$ (across assessment times). The primary hypothesis test will focus on the DRS-P assessments performed within the first 2 years of each patient's enrollment. In order to limit the overall type I error to 0.05 for the hypotheses $H_{C:E1,DRS}$ and $H_{C:E2,DRS}$, the type I error for each of these hypothesis tests will be 0.025 (two-tailed). If either of these null hypotheses are rejected then a treatment-by-assessment time interaction term will be added to the model in order to estimate and compare treatment difference at each assessment time. The comparisons (between the particular experimental group and the reference group) at the individual assessment-times will also be conducted with $\alpha=0.025$ (2 tail) for each time point.

Exploratory analyses will include an assessment of the model residuals in order to evaluate the adequacy of modeling assumptions.

Statistical Power for NFOSI-DRS-P

A previously conducted study involving 51 patients indicates that the expected mean and standard deviation of the NFOSI-DRS are approximately 51.6 and 10.7, respectively. The primary analysis of NFOSI-DRS will focus on the assessments scheduled during the first 2 years following enrollment onto the study. For the purposes of estimating power, it is assumed that there will be a 5% attrition of patients at each assessment time, due to death or non-compliance. Also, it is assumed that the correlation between two consecutive assessments on the same individual will be 0.60, and between two assessments separated by 1 and 2 assessments will be 0.40 and 0.20,

respectively. The correlation between scores more than 2 assessments apart is assumed to be 0.10. A simulation of 1000 trials indicates that there is 80% power to detect a difference in mean scores between treatment groups that increases linearly from 0 to 5 units over the first 2 years. If the null hypothesis concerning the comparison of the mean NFOSI-DRS scores between E2 and C (or E1 and C) is rejected, then temporal trends in the differences between treatment groups will be modeled in an exploratory fashion.

Treatment Related Symptoms and Other PRO Scales

There are no specific hypotheses and therefore no type I error allocation scheme for the wide-variety of potential treatment-related symptoms (TRS). The analyses of the TRS items contained in the NFOSI-18, the FACT/GOG-Ntx-4 scale and the EQ-5D primarily involves estimating mean scores, proportions or relative odds with confidence intervals for each treatment group. Identifying clinically relevant differences between treatment groups in these treatment-related symptom scores will be useful to future patients making treatment decisions based on results from this trial. See Appendix X for further detail on these analyses.

Missing PRO information

Patient death, noncompliance, missed clinic appointments, and patient illiteracy, can cause observations to be missed. One or more of the PRO assessments may be missing for an individual on any occasion. Missing information is troublesome particularly in studies involving repeated patient assessments. The frequency that assessments are missed will be monitored every 6 months throughout the study. Data Coordinators will be working with the Study Team and the NRG's Patient Reported Outcome Committee to identify reasons that data are missing and recommending remedial actions when possible.

The PRO instruments used in this study have been translated to several different languages. Women, who are unable to read or have difficulty reading, will not be required to participate in the PRO component of this study, however, a woman may elect to have the items read to her and be assisted in completing the instruments.

13.13 Translational Studies

13.13.1 BRCA1 or BRCA2 Mutations (07/31/2017)

It is expected that approximately 30% of the patients enrolled onto the study will have either a BRCA1 or BRCA2 mutation; however, these patients are expected to have a more favorable prognosis compared to those without these mutations. At the time of the final analysis approximately 384 (70%) of all patients enrolled onto the study will have experienced a PFS event. A proportional hazards model will be used to estimate the relative hazard of a

PFS event among patients with BRCA1 or BRCA2 mutations relative to those with no such mutations. If a BRCA1 or BRCA2 mutation decreases the risk of progression and death 30% (HR=0.70), this sample size provides 81% statistical power when the type I error is limited to 0.05 for a two-tail test.

The relative treatment efficacy in the subgroups of patients with or without germline BRCA1/2 mutation will be assessed by estimating the treatment hazard ratios and their corresponding confidence intervals within the subgroups with and without BRCA1/2 mutations. The treatment hazard ratios will be estimated from a multivariable proportional hazards model. At the time of the final analysis, there will be at least 265 PFS events for estimating the C vs E2 treatment hazard ratio and about the same number of PFS events for estimating the C vs E1 hazard ratio. Assuming that at least 20% of the PFS events have BRCA1/2 mutations then there will be about 53 events among those patients with mutations for estimating each of the treatment hazard ratios ($D_1=0.20*265=53$). Assuming that there are nearly an equal number of events in each treatment group, then the variances of the log treatment hazard ratios in the subgroup with BRCA1/2 mutations are approximately 0.0755 ($4/D_1=4/53$). Likewise, among those with no mutations the expected number of PFS events is 212 ($0.80*265$) and the variances of the log treatment hazard ratios are approximately 0.0189 ($4/D_2=4/212$).

13.13.2 BROCA-HR

Cancer cells may need to be not only deficient in HR but also proficient in the alternative (error-prone) non-homologous end joining (NHEJ) DNA repair pathway to be sensitive to a PARP inhibitor (PARPi). The BROCA-HR assay identifies mutations in genes that are involved in homologous repair (HR) or non-homologous end joining (NHEJ) as well as the presence of several clinically relevant SNPs. While the BROCA-HR assay consists of several laboratory measurements, the ultimate result classifies each individual as either positive (at least one of the pre-specified mutations or SNPs) or negative (no such mutations or SNPs). A single multivariable proportional hazards model (Cox, 1972) will be used to estimate the treatment hazard ratios (and standard deviations) for each of the experimental treatments relative to the reference treatment (chemotherapy) group. All of the patients with BROCA-HR assessments will be included in the analysis. The model will include indicator variable(s) for the randomly assigned treatment, and BROCA-HR status, as well as term(s) for the interaction(s) between these factors. The estimated hazard ratio(s) and their corresponding confidence intervals will be depicted with a forest plot, and assessed for qualitative interaction(s) (Gail and Simon, 1985). It is anticipated that 35% of the enrolled patients will have BROCA-HR deficiencies; however, these patients are expected to have a favorable prognosis compared to those patients without these deficiencies and so only about 25% ($D_1=0.25*265=66$) of the PFS events at the time of the final analysis are expected to have BROCA-HR

deficiencies. Therefore, the variances of the log treatment hazard ratios (C:E1 and C:E2) will be approximately 0.0606 ($4/D_1 = 4/66$). Among those without BROCA-HR deficiencies the variances are expected to be about 0.0202 ($4/(0.75*265)$).

The other measures of homologous repair deficiency or NHEJ such as BRCA1 methylation, or genomic scarring will be analyzed in a similar manner. Since these are exploratory objectives the primary focus is on the estimated treatment hazard ratios and confidence intervals for patient subgroups determined by their marker status. Forest plots will be used to display these results. Also, Kaplan-Meier (Kaplan and Meier, 1958) plots will be used to depict the estimated probability of survival for women in each treatment group by their marker status.

13.13.3 CEC

An increase in the level of circulating endothelial cells (CECs) is thought to be an early indicator for drug induced vascular damage. This component of the study seeks to determine whether the CEC levels that are measured after 3 days of treatment are independent of the treatment. Also, this study will assess whether the change in CEC levels between the pretreatment value and the value on the 3rd-day of treatment is prognostic. Finally, it will assess whether the prognostic effect size of the change in CECs levels depends the treatment (i.e. a predictive biomarker).

CEC level is a continuous measure. Based on 10 patients treated with olaparib or olaparib and cediranib from a previous study, the mean and standard deviation of pretreatment CEC(%) was $1.1 * 10^{-4}$ and $1.5 * 10^{-4}$, respectively. Three days following the initiation of treatment the mean and standard deviation were $1.3 * 10^{-4}$ and $1.6 * 10^{-4}$, respectively. The correlation between pre- and post-treatment values was -0.10. The CEC measurements from the current study will be used to better characterize the distributions of this biomarker prior to treatment and 3 days after initiating treatment for each of the treatment groups using histograms, rug-plots or box-plots. Extreme outliers will be noted. The first null hypothesis is that the distribution of the 3rd-day CEC values is independent of the treatment group assignment. An ANCOVA model (Kleinbaum, 1988) will be used to assess whether the 3-day CEC levels are independent of treatment. All of the patients will be included in this analysis, provided they have valid pre-treatment and 3rd-day CEC values. The ANCOVA model will include the randomly assigned treatment, pretreatment CEC values and age at study enrollment as covariates. Assuming valid measurements are available from 90% of the individuals in each treatment group ($0.90 * 183 = 164$), there is approximately 85% power to detect an effect size (difference in group means/standard deviation) of 0.30. If the global null hypothesis of no differences among treatment groups can be rejected with type I error set to 0.05, then pairwise comparisons between the

treatment groups will be performed. Sensitivity analyses will be performed to determine whether statistical significance is influenced by extreme outliers.

A proportional hazards model will be used to assess a linear association between the change in CEC values and the log relative hazard of first progression or death (PFS). For the primary analysis, the proportional hazards model will include randomized treatment group as a polychotomous covariate. Sensitivity analyses will include known prognostic factors in the model. At the time of the final analysis approximately 70% ($0.70 \times 549 = 384$) of the patients enrolled onto the study will have experienced a PFS event. This sample size provides 81% statistical power if the true reduction in the hazard of progression or death is 15% ($HR=0.85$) for individuals whose change in CEC values are one standard deviation higher (i.e., one standard deviation of the change in CEC values). A plot of the martingale residuals (Therneau, 2000) or estimated relative hazards by change in CEC quintiles will be used to qualitatively assess the assumption of a linear relationship between the change in CEC values and the log relative hazard.

13.13.4 Plasma Angiome

This component of the study will use a panel which has been developed through collaborative efforts from Duke University and Aushon BioSystems to measure 14 soluble angiogenic factors, 7 matrix derived factors, as well as, 7 markers of vascular activation and inflammation in patients' serum or blood. The goal is to assess these biomarkers individually for prognostic value and then develop a composite score that is based on these biomarkers which is prognostic. For these purposes, the study participants with analyzable specimens will be randomly separated into two mutually exclusive groups. Approximately half of the individuals will be assigned to a training group and the remaining individuals will be assigned to a validation group. The clinical data and the biomarker data from the individuals in the training group will be combined and used to assess the prognostic value of each biomarker individually and to construct a composite prognostic score. The prognostic value of a single biomarker with regard to PFS will be assessed with a proportional hazards model. Since the expected number of PFS events in the entire study at the time of the final analysis is 384, then the expected number of PFS events in the training set at this time is $384/2=192$. This sample size would provide 80% power when the true hazard of first progression or death (PFS) decreases 20% ($HR=0.80$) for individuals whose biomarker values are separated by one standard deviation and type I error is limited to 0.05 for a two-tail test. In this case, however, the probability of falsely declaring at least one biomarker as prognostic, when none of the biomarkers are associated with PFS, is 76%. (This underscores the need for a validation group.) Also, a putative prognostic score will be developed based on multivariate modeling and biologic knowledge about these biomarkers and their potential for interactions.

Prior to validating the composite putative prognostic score the team that developed the scoring procedure will prepare a document that completely and unambiguously defines scoring procedure and the validation procedure. Then, an independent statistician, who was not involved in the training phase, will be identified. This individual will review and confirm that the documentation for the scoring algorithm and validation procedure are unambiguous and appropriate. The independent statistician will also be responsible for maintaining this documentation in a secure location. The independent statistician will then either use computer code provided by the development team or develop the computer code from the documentation to score each individual in the validation data set and validate the putative prognostic score. If the validation process determines that the score is not clinically useful, then the development team may repeat this entire process to develop alternative scoring procedures. In this case, however, the independent statistician will be responsible for documenting each attempt to validate a new scoring procedure. Also, the clinical data from those patients who are in the validation group will not be transferred to the team involved in the training process. If the prognostic score is validated, then the independent statistician can release the validation documentation and the validation dataset for external verification.

14.0 PUBLICATION INFORMATION AND ADMINISTRATIVE AGREEMENTS

Under discussion with NRG leadership.

15.0 EVALUATION CRITERIA

Because of the differences in cycle lengths between the allowed regimens, tumor reassessment will be time-based, and not cycle-based, with CT scan or MRI performed once every 9 weeks (+/- 7 days), and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Imaging assessments can be discontinued if disease progression is confirmed according to RECIST 1.1. However, if a patient discontinues study treatment for any reason other than progression, imaging studies should continue every 9 weeks (+/- 7 days) until progression. After 2 years of protocol therapy or follow-up (measured from approximately cycle 1, day 1), imaging studies will be conducted every 12 weeks.

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.

15.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with reference or investigational therapy.

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

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.

15.2 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 by chest x-ray or as ≥ 10 mm 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 may be considered measurable if there has been interval progression since the time of radiation.

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

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

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

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

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

15.3 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 diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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.

15.4 Response Criteria

15.4.1 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. CA-125 must normalize for a patient to be considered in complete clinical response.

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. (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.

15.4.2 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 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).

15.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the date of randomization until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since randomization). The patient's best response assignment will depend on the measurement criteria.

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

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

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

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration.*” Every effort should be made to document the objective progression even after discontinuation of treatment.

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR

Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

15.4.4 Duration of Response

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

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

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

15.4.5 Evaluation of Biomarkers

For this study, a rise in CA-125 alone is not sufficient to declare progression, and progression events should be determined by radiographic evidence of progression.

15.4.6 Progression-Free Survival

PFS is defined as the duration of time from the date of randomization progression or death, whichever occurs first.

15.4.7 Time to First Subsequent Therapy (TFST) and time to Second subsequent therapy (TSST)

Time to first subsequent therapy is defined as the duration of time from randomization to initiation of a non-protocol, anti-cancer treatment (including cytotoxic, surgical, or radiotherapy) or death. Time to second subsequent therapy is defined as the duration of time from randomization to initiation of the second-line non-protocol, anti-

cancer treatment (including cytotoxic, surgical, or radiotherapy) or death.

16.0 REFERENCES

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APPENDIX I

PERFORMANCE SCALE

<u>GRADE</u>	<u>KARNOFSKY SCALE</u>	<u>PERFORMANCE</u>
0	90 & 100	FULLY ACTIVE
1	70 & 80	RESTRICTED IN PHYSICALLY STRENUOUS ACTIVITIES, BUT AMBULATORY.
2	50 & 60	AMBULATORY; CAPABLE OF SELF CARE; UNABLE TO WORK; UP 50% OF WAKING HOURS.
3	30 & 40	LIMITED SELF CARE; CONFINED TO BED OR CHAIR 50% OF WAKING HOURS.
4	10 & 20	COMPLETELY DISABLED; NO SELF-CARE

5/30/76

APPENDIX II – PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD (11/07/2016)

OLAPARIB

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 (AZD2281)**. This clinical trial is sponsored by the National Cancer Institute (NCI). 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 prescriber need to know:

Olaparib interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4/5, 1A2, 2B6, 2C9, 2C19 and UGT1A1. Olaparib is cleared by CYP3A4/5 and is affected by strong and moderate inhibitors and inducers of CYP3A4/5. Olaparib inhibits CYP3A4 and UGT1A1 enzymes and may increase levels of other drugs that are cleared by these enzymes. Olaparib induces CYP 1A2, 2B6 and 3A4 enzymes and has the possibility of inducing CYP 2C9, 2C19 enzymes that may result in decreased levels of other drugs that are cleared by these enzymes.
- The transport proteins in question are P-glycoprotein (P-gp), organic anion-transporting polypeptides (OATP1B1 and OAT3), organic cation transporters (OCT1 and OCT2), multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and breast cancer resistance protein (BCRP). Olaparib requires P-gp to move in and out of cells and concomitant administration of strong P-gp inhibitors and inducers should be avoided. Olaparib inhibits P-gp, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K transporters and has the possibility of inducing P-gp and that may affect the transport of other drugs that depend on these proteins to move in and out of cells. Use caution when taking substrates of these transporters, such as statins.

November 2015

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 many drugs which can cause side effects. Because of this, it is very important to tell your study doctors about all of your medicines before you enroll on this clinical trial. It is also very important to tell them 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 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. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care prescribers can write prescriptions. You must also tell 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 need certain liver enzymes and transport proteins to be effective or to be cleared from your system. 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 of CYP3A4/5 and P-gp.” Olaparib inhibits enzymes “CYP3A4, UGT1A1, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP.” Olaparib possibly induces “CYP 1A2, 2B6, 3A4, 2C9, 2C19 and P-gp.” These characteristics may change how other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit, grapefruit juice and Seville oranges while taking olaparib.
- You may need to be monitored more frequently if you are taking any drugs that have narrow therapeutic ranges.
- 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

November 2015

<p>STUDY DRUG INFORMATION WALLET CARD</p> <p>You are enrolled on a clinical trial using the experimental drug olaparib (AZD2281). This clinical trial is sponsored by the NCI. Olaparib interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:</p> <ul style="list-style-type: none">➢ Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) that you are taking part in a clinical trial.➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.➢ Olaparib interacts with liver enzymes, CYP3A4/5, 1A2, 2B6, 2C9, 2C19, UGT1A1, and transport proteins, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP.	<ul style="list-style-type: none">➢ Olaparib must be used very carefully with other medicines that interact with these enzymes and proteins.➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered “strong or moderate inducers/inhibitors of CYP3A4/5 and P-gp.” Olaparib inhibits “CYP 3A4, UGT1A1 and transport proteins P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP and induces CYP 1A2, 2B6, 3A4, 2C9, 2C19 and transport protein P-gp.” It may change how other medicine works in your body.➢ Before prescribing new medicines, your regular health care providers should go to a frequently updated medical reference for a list of drugs to avoid, or contact your study doctor.➢ Your study doctor’s name is _____ and can be contacted at _____.
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CEDIRANIB

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, **AZD2171 (cediranib)**. This clinical trial is sponsored by the National Cancer Institute (NCI). 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 prescriber need to know:

AZD2171 (cediranib) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4, 2D6, flavin-containing monooxygenase (FMO) and UGT1A4. AZD2171 (cediranib) is metabolized by FMO1, FMO3 and UGT1A4 and may be affected by other drugs that strongly inhibit or induce these enzymes. AZD2171 (cediranib) weakly inhibits CYP 2D6 and 3A4 and may increase levels of affected substrates.
- Cediranib (AZD2171) may induce gastrointestinal CYP3A and UGT enzymes, therefore potentially reducing the effectiveness of hormonal contraceptives
- The transport proteins in question are P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). AZD2171 (cediranib) requires P-gp to move in and out of cells. Cediranib (AZD2171) inhibits BCRP, P-gp, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K and this may affect the clearance of other drugs that are dependent on these transport proteins.
- AZD2171 (cediranib) is 95% protein bound (human serum albumin and alpha-1-acid glycoprotein) and may displace other highly protein-bound drugs. Use caution in patients taking concomitant medications with narrow therapeutic ranges.
- Patients receiving AZD2171 (cediranib) are at increased risk of bleeding and hemorrhage. Increase monitoring in patients who also receive anticoagulation therapy.

June 2016

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

Cediranib (AZD2171) interacts with many drugs which can cause side effects. Because of this, it is very important to tell your study doctors about all of your medicines before you enroll on this clinical trial. It is also very important to tell them 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 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. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care prescribers can write prescriptions. You must also tell 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:

AZD2171 (cediranib) must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. 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 of FMO1, FMO3, UGT1A4 and P-gp.” Cediranib (AZD2171) inhibits enzymes “CYP 2D6 and 3A4, transport proteins BCRP, P-gp, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K and is highly protein-bound.” These characteristics may change how other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Cediranib (AZD2171) can increase the risk of bleeding and interferes with wound healing. Let your doctor know if you recently had or are planning to have any surgery.
- 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

_____.

June 2016

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental drug **AZD2171 (cediranib)**. This clinical trial is sponsored by the NCI. AZD2171 (cediranib) interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistant, nurse practitioners, pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- AZD2171 (cediranib) interacts with CYP3A4, 2D6, FMO1, FMO3,

UGT1A4 and transport proteins, P-gp and BCRP and must be used very carefully with other medicines that interact with these enzymes and proteins.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered “strong inducers/inhibitors of FMO1, FMO3, UGT1A4 and P-gp.” Cediranib (AZD2171) inhibits “CYP 2D6 and 3A4 and transport proteins BCRP, P-gp, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K and is highly protein-bound.” It may change how other medicine works in your body..
- Before prescribing new medicines, your regular health care providers should go to [a frequently-updated medical reference](#) for a list of drugs to avoid, or contact your study doctor.
- Your study doctor’s name is _____ and can be contacted at _____.

The following tables list CYP3A4 inducers and inhibitors. Investigators should consult a frequently updated drug information reference for a list of strong inducers and prohibitors.

CYP3A4 Inducers (prohibited)

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

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

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

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

³Weak inhibitor per Lacy et al. May be used with caution.

Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

CYP3A4 Inhibitors

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

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

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

Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

APPENDIX III – Oral Antihypertensive Medications (11/07/2016)

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with cediranib through CYP450. Agent classes are listed in order of preference in the absence of any other compelling indication, such as impaired renal function, proteinuria, etc. Note that each agent’s dosing should be maximized before being replaced or adding another agent class.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	Yes (CYP450 unknown)
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	5 mg daily	10-20 mg daily	40 mg daily	No
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes, but not CYP450
	Rarely used: perindopril	4 mg daily	none	8 mg daily	Yes, but not CYP450
	Rarely used: quinapril	10 mg daily	20 mg daily	40 mg daily	No
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 and 2C9 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate

	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	40 mg daily	none	80 mg daily	Yes, but not CYP450
	valsartan	80 mg daily	none	160 mg daily	Yes, but not CYP450
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	25 mg daily	50 mg daily	100 mg daily	No
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	CYP 3A4 substrate
α and β Blocker	labetalol	100 mg twice daily	200 mg twice daily	400 mg twice daily	Yes, but not CYP450
Diuretics	Hydralazine	10 mg four times daily	25 mg four times daily	50 mg four times daily	no
	Hydrochlorothiazide	12.5 mg AM daily	25 mg AM daily	50 mg AM daily	no
	Furosemide	20 mg daily	20 mg twice daily	40 mg twice daily	no
Nitrates	Isosorbide dinitrate ER	40 mg daily	40 mg twice daily	80 mg twice daily	CYP 3A4 substrate

	Isosorbide mononitrate ER	30 mg AM daily	60 mg AM daily	90 mg AM daily	CYP 3A4 substrate
Dihydropyridine Calcium-Channel Blockers (DHP CCB)	nifedipine XL	30 mg daily	60 mg daily	90 mg daily	CYP 3A4 substrate
	amlodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate

APPENDIX IV – CARBOPLATIN DOSE CALCULATION INSTRUCTIONS

- 1) The Cockcroft-Gault formula will be used in GOG trials.
- 2) Conversion of IDMS creatinine levels to “non-IDMS” values will not be permitted.
- 3) The carboplatin calculation tool is available on the GOG website (Web Menu, Tools).

Dosing of Carboplatin:

- 1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.
- 2) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.
- 3) Carboplatin doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.
- 4) At the time of dose modification, if the patient’s age had changed (the patient has had a birthday), the site can use the current age.
- 5) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a **minimum value of 0.7 mg/dl**. For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC x (GFR + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.

Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed doses of carboplatin are:

AUC 6 = 900 mg

AUC 5 = 750 mg

AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\text{Creatinine Clearance (mL/min)} = \frac{[140 - \text{Age (years)}] \times \text{Weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dl)}}$$

Notes:

1) Weight in kilograms (kg):

- a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: <http://www.nhlbisupport.com/bmi/>
- b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
- c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.
- d. Adjusted weight calculation:
Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) + 45.5
Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity: If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

APPENDIX V – TRANSLATIONAL SCIENCE SPECIMEN PROCEDURES (07/31/2017)

I. Obtaining a Bank ID for Translational Science Specimens (11/07/2016)

Only one Bank ID (#### - ## - G ###) is assigned per patient. All translational science specimens and accompanying paperwork must be labeled with this coded patient number.

A Bank ID is automatically assigned once the Specimen Consent is completed and indicates that a patient has agreed to participate in the translational science component. If a patient has previously been assigned a Bank ID, please ensure the Bank ID appearing in Rave is the same as the previously assigned Bank ID.

Please contact User Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@nrگونcology.org; Phone: 716-845-7767).

II. CEC Whole Blood (11/07/2016)

Shipped to the Preclinical Development Research Core

A. Requesting CEC Whole Blood Specimen Kits

CPT (citrate) tubes will be provided by the NRG Oncology Biospecimen Bank-Columbus for the collection of CEC whole blood specimens. **Specimen kits are not provided for the shipment of CEC whole blood specimens to the Preclinical Development Research Core (PDRC), but the collection tubes are shipped to sites in the Research Plasma kits. Sites must provide their own shipping kits and cover shipping costs. Do not ship CEC whole blood specimens to the PDRC using any of the specimen kits provided by the NRG BB-Columbus.**

B. Labeling CEC Whole Blood

A waterproof permanent marker or printed label should be used to label each translational science whole blood specimen with:

Bank ID (#### - ## - G ###)
protocol number (NRG - GY ###)
specimen code (WB02 for pre-treatment, WB03* for C1D3)
collection date (mm/dd/yyyy)

**WB03 should be collected only if WB02 was submitted.*

C. CEC Whole Blood

1. Label the CPT (citrate) collection tube as described below. **Note: CPT (citrate) tube should be at room temperature (i.e., 18-25°C).**
2. Draw 8mL of blood into the labeled CPT (citrate) tube.
3. Immediately after collection, gently invert the tube 6 times to mix the blood and citrate.
4. CEC whole blood should be stored upright at room temperature until the specimen can be shipped. Ship to the PDRC the day the specimen is collected. If the CEC whole blood absolutely cannot be shipped the day it is collected, the tube should be kept at room temperature until the specimen can be shipped the next day. **Note: The laboratory**

testing to be done is time sensitive. CEC whole blood specimens must be shipped the day the specimen is collected. If the specimen absolutely cannot be shipped the same day, a note detailing why the specimen needed to be shipped the next day must be included. If the specimen cannot be shipped within 24 hours, it should be discarded.

D. Shipping CEC Whole Blood Specimens

CEC whole blood specimens should not be shipped until after patient registration and Bank ID assignment.

An electronically completed copy of Form TR must be included for each CEC whole blood specimen.

CEC whole blood specimens should be shipped using your own container at your own expense directly to:

Preclinical Development Research Core

NCI, NIH

Bldg 10, Rm 12N218

10 Center Dr

Bethesda, MD 20892

Phone: 301-496-1547

Emails: trepel@helix.nih.gov, leesun@mail.nih.gov, leemin@mail.nih.gov,
akira.yuno@nih.gov

Note: Please notify the PDRC (via the four email addresses provided) when a patient is scheduled for a blood draw and when the specimen will be shipped. The FedEx tracking number should be included in the shipment.

CEC whole blood specimens can be shipped to the PDRC **Monday through Thursday for Tuesday through Friday delivery**. Do not ship whole blood the day before a government holiday. Use your own shipping container to ship specimens via **FedEx priority overnight**.

III. Translational Science Specimens (11/07/2016)

Shipped to the NRG Oncology Biospecimen Bank-Columbus (NRG BB-Columbus)

A. Requesting Translational Science Specimen Kits

Specimen kits are no longer provided for the collection and shipment of **BROCA-HR whole blood and FFPE specimens** shipped to the NRG BB-Columbus. *Please note the updated specimen collection procedures below.*

Kits will be provided for the collection and shipment of **frozen specimens**.

Two research plasma kits will be provided per patient. **Research Plasma** kit contents are the same for all patients, regardless of the arm to which the patient is randomized. The Research Plasma kit can be ordered when a potential patient is identified. The **Final Research Plasma** kit should not be ordered until the time of disease progression or end of treatment.

The **Arm II PK** or **Arm III PK** kit should be ordered after randomization, as contents are dependent on the arm to which the patient is randomized. The Arm II and Arm III PK kits should be used to ship the Future Use Whole Blood (WB04), in addition to the PK plasma specimens.

***Note:** CPT (citrate) tubes will be provided by the NRG BB-Columbus for the collection of CEC whole blood specimens. These tubes are included in the **Research Plasma kit** and are not ordered separately. Specimen kits are not provided for the shipment of CEC whole blood specimens to the PDRC. Sites must provide their own shipping kits and cover shipping costs.*

Sites can order kits online via the Kit Management link (<https://ricapps.nationwidechildrens.org/KitManagement/>). Each site may order two kit types per protocol per day (daily max = 6 kits).

Please contact the NRG BB-Columbus if you need assistance (Email: BPCBank@nationwidechildrens.org; Phone: 866-464-2262).

Be sure to plan ahead and allow time for kits to be shipped by ground transportation. Kits should arrive within 3-5 business days.

Note: Unused materials and kits should be returned to the NRG BB-Columbus.

B. Labeling Translational Science Specimens

A waterproof permanent marker or printed label should be used to label each translational science specimen with:

Bank ID (#### - ## - G ###)
protocol number (NRG - GY ###)
specimen code (see protocol section 11.2.1)
collection date (mm/dd/yyyy)
surgical pathology accession number (tissue specimens only)
block number (tissue specimens only)

Note for tissue specimens: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

C. BROCA-HR Whole Blood

1. Label the lavender/purple top (EDTA) collection tube(s) as described below. Multiple tubes may be used to collect the required amount.
2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.

4. Ship whole blood to the NRG BB-Columbus the day the biospecimen is collected. If the whole blood **absolutely** cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) and shipped within 24 hours.

D. Formalin-Fixed, Paraffin-Embedded (FFPE) Tissue

1. BROCA-HR FFPE: Patients must agree to submit this mandatory specimen.

BROCA-HR FFPE tissue should be the most representative of the specimen type (primary, metastatic). BROCA-HR primary (FP02) or metastatic (FM02) tumor should be collected prior to all treatment.

Two consecutive unstained slides (charged, 10µm) must be provided.*

**If patient consents to the optional FFPE collection (specimen codes ending in “01”; section 11.2.1.2) and a block will be submitted on a permanent basis to fulfill both the mandatory (specimen codes ending in “02”; section 11.2.1.1) and optional (specimen codes ending in “01”; section 11.2.1.2) specimen requirements, then label the block with the specimen code ending in “01.” Complete and ship both the “01” and “02” specimen transmittal forms (i.e., Form TR) with the block.*

2. OPTIONAL FFPE

FFPE tissue should be the most representative of the specimen type (primary, metastatic, recurrent). Only one block may be submitted per tissue type.

- **Primary** and **metastatic** tumor should be collected prior to all treatment.
- **Primary neoadjuvant treatment** and **metastatic neoadjuvant treatment** tumor (collected after the patient received neoadjuvant treatment) should only be submitted if tumor collected prior to all treatment is not available.
- **Recurrent** tumor should be collected prior to the study treatment. Recurrent tumor collected from the site of primary disease should be labeled **recurrent primary**. Recurrent tumor collected from a site other than the site of primary disease (e.g., lymph node) should be labeled **recurrent metastatic**.

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 22 unstained slides* (**2 charged, 10µm**; 10 charged, 5µm; and 10 uncharged, 10 µm) should be submitted. All tissue sections should be cut sequentially from the same block.

**Note: BROCA-HR FFPE tissue is a mandatory specimen requirement. If submitting slides, the two (charged, 10µm) unstained sections required for BROCA-HR testing should be cut first, followed by the 20 unstained sections (10 charged, 5µm and 10 uncharged, 10µm) for the optional translational science.*

Completing Form TR for FFPE

The type of specimen (block, slides) should be specified on Form TR. If submitting slides, the slide type, thickness, and count should also be specified.

If patient consents to the optional FFPE collection (specimen codes ending in “01”; section 11.2.1.2) and a block will be submitted on a permanent basis to fulfill both the mandatory (specimen codes ending in “02”; section 11.2.1.1) and optional (specimen codes ending in “01”; section 11.2.1.2) specimen requirements, then label the block with the specimen code ending in “01.” Complete and ship both the “01” and “02” specimen transmittal forms (i.e., Form TR) with the block. Complete the “01” Form TR as “collected” and include all requested specimen information. Complete the “02” Form TR as “not collected” and specify “submitted for another study.”

All FFPE tissue should be submitted with the corresponding pathology report.

E. Future Use Whole Blood

1. Label the purple top (EDTA) blood collection tube(s) as described below. Multiple tubes may be used to collect the required amount. **Do not use glass blood collection tubes.**
2. Draw 7-10mL of blood into the purple top (EDTA) tube(s). A minimum of 3mL is needed for processing.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.
4. Immediately **freeze the whole blood in an upright position** in a -70°C to -80°C freezer or by direct exposure with dry ice until ready to ship. If a -70°C to -80°C freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

F. Olaparib PK Plasma

Note: The laboratory testing to be done is time sensitive. Plasma must be processed within one hour of collection. Blood may remain at room temperature until processed.

1. Label one cryovial as described below. Use a 2mL cryovial as plasma will be shipped to the NRG Oncology Biospecimen Bank-Columbus.
2. Draw **2mL** of blood into **2mL green top (lithium heparin)** tube. **Be sure to fill the blood collection tube completely.**
3. Immediately after collection, gently invert the blood collection tube 8-10 times to mix the blood and heparin.
4. Centrifuge the blood at 1500-2000g for 15 minutes to separate the plasma (top, straw-colored layer) from the red blood cells (bottom, red layer).
5. Quickly, transfer the plasma into the pre-labeled cryovial and cap the tubes securely. Place all plasma into the one cryovial.
6. Immediately **freeze the plasma in an upright position** in a -70°C to -80°C freezer or by direct exposure with dry ice until ready to ship. If a -70°C to -80°C freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

Completing Form TR for Olaparib PK Plasma

Green top (lithium heparin) tubes must be used for the collection of blood used to process olaparib PK plasma biopsecimens. When completing Form TR, select “Other” for tube type and specify “lithium heparin.”

G. Cediranib PK Plasma

Note: The laboratory testing to be done is time sensitive. Plasma must be processed within one hour of collection. Blood may remain at room temperature until processed.

1. Label one cryovial as described below. Use a 2mL cryovial as plasma will be shipped to the NRG Oncology Biospecimen Bank-Columbus.
2. Draw **2mL** of blood into **2mL purple top (K2EDTA)** tube. **Be sure to fill the blood collection tube completely.**
3. Immediately after collection, gently invert the blood collection tube 8-10 times to mix the blood and EDTA.
4. Centrifuge the blood at 1500-2000g for 15 minutes to separate the plasma (top, straw-colored layer) from the red blood cells (bottom, red layer).
5. Quickly, transfer the plasma into the pre-labeled cryovial and cap the tubes securely. Place all plasma into the one cryovial.
6. Immediately **freeze the plasma in an upright position** in a -70°C to -80°C freezer or by direct exposure with dry ice until ready to ship. If a -70°C to -80°C freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

H. Research Plasma

Note: The laboratory testing to be done is time sensitive. Plasma must be processed within one hour of collection.

1. Label cryovials and a 15mL conical tube as described above. Use 2mL cryovials as plasma will be shipped to the NRG Oncology Biospecimen Bank-Columbus.
2. Draw 7-10mL of blood into lavender/purple top (EDTA) tube(s).
3. Immediately after collection, gently invert the blood collection tube 5-10 times to mix the blood and EDTA.
4. Centrifuge the blood at 1000g for 15 minutes at 4°C (preferred) or room temperature to separate the plasma (top, straw-colored layer) from the red blood cells (bottom, red layer).
5. Transfer the plasma into a pre-labeled 15mL conical tube and gently mix.
6. **Centrifuge the plasma again at 1000g for 15 minutes at 4°C (preferred) or room temperature.**
7. Quickly, evenly dispense (aliquot) the plasma into the pre-labeled cryovials and cap the tubes securely. Place a minimum of 0.25mL into each cryovial. **Avoid any residual cells that pellet at the bottom of the conical tube.**
8. Immediately **freeze the plasma in an upright position** in a -70°C to -80°C freezer or by direct exposure with dry ice until ready to ship. If a -70°C to -80°C freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

**If the Pre-Treatment Research Plasma (PB09) biospecimen is not collected, the subsequent Research Plasma (PB10 and PB11) biospecimens should not be collected.*

I. Shipping Translational Science Specimens

Translational science specimens should not be shipped until after patient registration and Bank ID assignment.

An electronically completed copy of Form TR must be included for each translational science specimen.

All translational science specimens should be shipped to:

NRG BB-Columbus / Protocol NRG GY004
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: 614-722-2865
FAX: 614-722-2897
Email: BPCBank@nationwidechildrens.org

1. FFPE Tissue

FFPE tissue, an electronically completed copy of Form TR, and a copy of the corresponding pathology report should be shipped using your own container at your own expense to the NRG BB-Columbus (address above).

Do not ship FFPE tissue for Saturday delivery.

2. BROCA-HR Whole Blood

Whole blood biospecimens should be shipped to the NRG BB-Columbus (address above).

Whole blood biospecimens can be shipped to the NRG -Columbus **Monday through Friday for Tuesday through Saturday delivery**. Do not ship whole blood the day before a holiday. Use your own shipping container to ship biospecimens via **FedEx priority overnight**.

When shipping whole blood biospecimens, **your site must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the NRG BB-Columbus at BPCBank@nationwidechildrens.org or by phoning 866-464-2262.

To ship whole blood biospecimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping whole blood biospecimens from more than one patient, please put each biospecimen in a separate plastic zip-lock bag before placing the biospecimens in the shipping bag. You may include up to four different blood biospecimens in one biohazard envelope.*

If you do not have these materials available at your site, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

Shipping Whole Blood Using Your Own Shipping Container

1. Place the whole blood biospecimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.
2. Wrap the biohazard envelope in bubble wrap or another padded material.

3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.
4. Place the Tyvek envelope in a sturdy shipping container (e.g., cardboard FedEx box).
5. Insert a copy of Form TR for each biospecimen.
6. Attach an Exempt Human Specimen sticker to the outside of the shipping container.
7. Print a pre-paid FedEx air bill using the Kit Management link (<https://ricapps.nationwidechildrens.org/KitManagement/>). Attach the air bill.
8. Make arrangements for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

3. Frozen Specimens

Frozen plasma and future use whole blood should be shipped using the specimen kit provided to the NRG BB-Columbus (address above).

Frozen specimens should be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship frozen specimens on Friday or the day before a holiday. Note: Saturday delivery is not available for frozen specimens.

Frozen specimens should be stored in an ultra-cold freezing/storage space (i.e., ultra-cold $\leq -70^{\circ}\text{C}$ freezer, liquid nitrogen, or direct exposure with dry ice) until the specimens can be shipped.

Shipping Frozen Translational Science Specimens in a Single Chamber Kit

1. Pre-fill the kit chamber about 1/3 full with dry ice.
2. Place the frozen specimens from each time point in a separate zip-lock bag.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Do not put more than 25 cryovials in a single chamber kit. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes.
4. Place the Tyvek envelope containing the frozen specimens into the kit and fill the chamber to the top with dry ice.
5. Insert a copy of Form TR for each specimen.
6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber.
7. Print a pre-paid FedEx air bill using the Kit Management system (<https://ricapps.nationwidechildrens.org/KitManagement/>). Attach the air bill.
8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.
9. Arrange for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

IV. Submitting Form TR

An electronically completed copy of Form TR must accompany each specimen shipped to the NRG BB-Columbus or alternate laboratory. Handwritten forms will not be accepted.

Note: A copy does not need to be sent to the NRG BB-Columbus or alternate laboratory if specimens are not collected.

Form TR should be printed from the Translational Research Form screen in Rave using the **"PDF File" link at the top of the form**. Clicking this link will generate a single page PDF. Do

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not use the “Printable Version” or “View PDF” links at the bottom of the form or any other method, as these formats will not be accepted.

Retain a printout of the completed form for your records.

Please contact User Support if you need assistance (Email: support@gogstats.org; Phone: 716-845-7767).

V. Banking Translational Science Specimens for Future Research

Specimens will remain in the NRG BB-Columbus and made available for approved research projects if the patient has provided permission for the use of her specimens for future health research.

Note: Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The patient’s specimen consent choices will be recorded on the signed informed consent document and electronically via Specimen Consent form. At the time of specimen selection for project distribution, the most recent consent information will be used.

Sites can amend a patient’s choices regarding the future use of her specimens at any time if the patient changes her mind.

If the patient revokes permission to use her specimens, the NRG BB-Columbus will destroy or return any remaining specimens. The patient’s specimens will not be used for any further research; however, any specimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens distributed prior to revoking consent.

Note: If return of specimens is requested, shipping will be at the site’s expense.

APPENDIX VI – TRANSLATIONAL SCIENCE LABORATORY TESTING PROCEDURES

I. BROCA-HR

A. Overview

The Swisher laboratory has previously published methodology and validation experiments for targeted capture and massively parallel sequencing of cancer genes (1-5). In brief, DNA will be extracted from peripheral blood mononuclear cells (PBMCs) and formalin-fixed, paraffin-embedded (FFPE) tumor containing at least 30% tumor nuclei. A targeted capture and massively parallel sequencing approach called BROCA will be applied to samples.

For the proposed study, a more recent version of BROCA with 55 genes (BROCA-HR; Table 1) that serve as a single assay to test for inherited risk of ovarian carcinoma and 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.

Table 1: BROCA-HR Genes

ATM	BRCC3	ERCC1	FANCG	MLH1	PAXIP1	RAD51	SMARCA4	XRCC3
ATR	BRE	ERCC4	FANCI	MRE11A	PIK3CA	RAD51	TOPBP1	XRCC4
BABAM1	BRIP1	FAM175A	FANCL	MSH2	PMS2	RAD51C	TP53	XRCC5
BAP1	CDH4	FANCA	FANCM	MSH6	POLD1	RAD51D	TP53BP1	XRCC6
BARD1	CDK12	FANCB	GEN1	NBN	POLE	RBBP8	UIMC1	
BLM	CHEK1	FANCC	HELQ	NEIL1	PPM1D	RIF1	USP28	
BRCA1	CHEK2	FANCD2	ID4	PALB2	PRKDC	RINT1	WRN	
BRCA2	DCLRE1C	FANCF	LIG4	PARP1	PTEN	SLX4	XRCC2	

Paired-end libraries with 350bp inserts will be prepared from 1ug of constitutional or neoplastic DNA and hybridized to a custom pool of oligonucleotides targeting genomic regions as previously described (2) 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 nucleotide variants and insertions and deletions will be detected as previously described with some updates in the bioinformatics pipeline (2). Deletions and duplications of exons will be detected by a combination of depth of coverage and split read analysis as previously described (3), supplemented with additional alignments generated by SLOPE (6). 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 platinum or PARPi on the trial. Later, in exploratory analyses, the Swisher laboratory will add in analyses of NHEJ and other modifying genes, genomic scarring, or other somatic tests by their lab or others to complement the determination of HR deficiency.

B. Laboratory Testing Procedures

Assay and Specimen Parameters: If sample is fluid (blood, ascites, pleural, cyst or other fluid, samples will be initially stabilized with acid citrate dextrose, and both fixed (with 10% neutral buffered formalin) and frozen types of tumor specimens will be used for BROCA-HR testing. Minimum 3 micrograms of DNA from blood, or 2 tumor sections by 1 cm diameter and 10 microns thickness will be required. An adjacent tissue section will be stained and examined by H&E to assess cellularity and tumor content; reference images of the H&E section will be kept and % cells that are tumor cells are reported as tumor content. Macrodissection will be used to enrich the sample for tumor cells.

Design of Mutation Assay and Data Analysis: Swisher laboratory has fully automated library preparation to increase sample turnaround and lower cost. Agilent 2200 TapeStation will be used to assess DNA concentration. DNA purity will be assessed using Agilent 2200 TapeStation and DNA integrity will be evaluated using Agilent Bioanalyzer. Swisher laboratory will prepare paired-end libraries with ~200 bp inserts from 300 ng of constitutional DNA and hybridize to a custom pool of oligonucleotides for the genomic regions listed above (3) 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 will be sequenced on a single lane of a HiSeq flowcell (Illumina) in rapid mode with 2x101 base pair paired end reads and a 7 base pair index read. Sequencing reads will be processed from real-time base calls with RTA 1.17.20 (Bustard) and converted to qseq.txt files in house on a Dell PowerEdge R900 server. Following demultiplexing, the reads will be aligned to the human reference genome (hg19) using BWA36. Duplicate reads and those not mapping within 2 standard deviations of the 250bp insert size will be removed. Variants will be identified using GATK37 after indel realignment and base quality recalibration. Variants from low quality (≤ 50) and depth of coverage regions (< 5 reads) are filtered out. Single nucleotide variants and insertions and deletions will be detected as previously described (3). Deletions and duplications of exons will be detected by a combination of depth of coverage and split read analysis as previously described (1), supplemented with additional alignments generated by split read algorithms (6). Missense mutations and in-frame deletions will only be classified as deleterious if a specific functional assessment has been carried out (i.e., BRCA1 C61G, RAD51C Q143R (7, 8)). Swisher laboratory will continue to update bioinformatics pipeline and integrate new alignment algorithms as they become available.

Data Reports and Assay Accuracy: Assay results will be reported as “Positive for mutation”. Swisher laboratory has established assay accuracy by comparison to a reference method (Sanger Sequencing, MLPA) and using reference materials (e.g. specimens with a variety of known mutations). For true positive; Swisher laboratory has verified mutations with Sanger Sequencing in 500 cases. For true negative; there were no false positives in >2000 samples tested to date and verified with Sanger sequencing. False positives have only been verified when they decrease the read count and/or quality limits in order to increase sensitivity in tumor samples, in this case Swisher laboratory always verify the mutation with Sanger sequencing and they usually do, the total number of samples: 2000. Swisher laboratory has shown >99% of concordance for within-run repeats and >99% of concordance for between-run repeats. With regard to limit of detection ((lowest amount of analyte that gives an informative result), Swisher laboratory has demonstrated that the lowest 5% of mutant or variant allele could be reliably detected in a wild type background.

C. References

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II. Circulating Endothelial Cells (CECs)

A. Overview

Whole blood (8mL) will be collected in CPT citrate tubes (Becton Dickinson and Company, Franklin Lakes, NJ) pre-treatment and on cycle 1, day 3 of treatment. The samples will be kept at ambient temperature and shipped overnight at ambient temperature the day the specimen is collected. The sample is stable up to 24 hours at room temperature.

After processing for viable freezing, the samples are frozen at -80°C and then stored in liquid nitrogen and stored in liquid nitrogen until use, per Trepel laboratory SOP (details below). Each patient sample is assigned a unique 2D barcode identifier. Flow cytometric analysis is performed as a batch analysis due to the necessity of running each patient's pre-therapy and post-therapy samples contemporaneously and to minimize variability due to different runs, reagents, and ambient conditions.

Peripheral blood mononuclear cells (PBMCs) isolated and viably frozen from patients will be analyzed; a minimum of 1×10^5 cells is required for each analysis. CECs will be analyzed on a MACSQuant flow cytometer (Miltenyi Biotec, Bergisch Gladbach, Germany) and analyzed using FlowJo software (FlowJo LLC, Ashland, OR). CEC assay components include fluorochrome-conjugated antibodies (CD45 (Clone HI30, BioLegend, San Diego, CA), CD31 (Clone WM59, BD Biosciences), CD105 (Clone 43A3, Biolegend), CD146 (Clone P1H12, EMD Millipore, Billerica, MA), CD133 (Clone A133, Miltenyi Biotec), mouse IgG1 isotype controls (Clone DD7, Millipore; Clone IS5-21F5, Miltenyi Biotec)), Hoechst 33342 (Life Technologies, Thermo Fisher Scientific, Carlsbad, CA), MACSQuant™ calibration beads (Miltenyi Biotec), FcR blocking reagent (Miltenyi Biotec), 7-AAD Viability Stain (BioLegend) and Quantum® R-PE MESF beads (Bangs Laboratories, Fishers, IN). Viability is defined by the absence of 7-aminoactinomycin D (7-AAD) staining, and analysis will be restricted to nucleated cells by

gating on Hoechst 33342-positive cells. These findings will be correlated with clinical results.

With regard to positive and negative controls for within-run repeats and for between-run repeats, Trepel laboratory will run bead standards that represent different quantal levels of fluorescence to provide a measure of immunofluorescence in different channels that can be used from one run to another. Trepel laboratory also runs isotype control samples for different fluorophores that provide standardization from one run to another. This analytical assay has been employed in multiple clinical trials (4-6).

The time points (pretreatment and on day 3 of treatment) were selected as Lee and colleagues have demonstrated predictive value of CECs in response to olaparib/cediranib combination in the recently reported phase II study of olaparib and cediranib (Lee et al., in press, *Frontiers in Oncology*, 2015).

Preanalytical and analytical variables: it is possible that there may be false positive or negative values of CECs due to cryopreservation/thawing process, inadequate identification of CECs from other hematopoietic cells or the suboptimal number of cells.

In clinical trial settings, PBMCs are collected from patients over time after which they are examined in a batched setting. It has been known that freezing and thawing affects the number of viable cells, measured by a multiparametric flow cytometry assay; an approximately 25% reduction in the number of viable cells from frozen samples compared to fresh PBMC samples ($p < 0.05$). (1). Trepel Lab has run a pilot experiment to examine percentages of CEC and CEP per viable PBMCs on fresh and viably frozen samples and did not observe significant difference between fresh and viably frozen PBMC samples. Trepel Lab will run pre and post-therapy samples together, and thus they will be under the same conditions to minimize variables (e.g. alignment and power of three lasers, microfluidics, FBS lots, antibody lots, etc). Further, CD45 (leukocyte common antigen) will be used to identify hematopoietic cells. CD31, CD133 and CD146 will be used to characterize endothelial subpopulations and EpCAM/CD326 will be used to separate WBC from circulating tumor cells (CTC). It has been well known that the values of CEC were significantly higher in patients with metastatic cancer compared to healthy donor ($p < 0.001$; ref 2). Jacques and colleagues reported the values of CECs in healthy individuals and metastatic cancer patients. There, the median CEC count was 6.5/mL (range, 0–15) in 20 healthy individuals and was 15.0/mL (mean \pm SD, 25.6 \pm 31.9; range, 0–179) in 125 patients with metastatic cancer, which are consistent with numbers Trepel lab has observed. Lastly, measuring CEC in PBMCs using 500,000 cells per sample has been highly reproducible (2, 4). For this study, where the sample is dedicated to identifying and quantifying only CECs, the Trepel Lab will run at least 500,000 events (cells) per sample. 8 mL whole blood will be collected in CPT citrate tube and thus at least 500,000 cells to be examined.

B. Laboratory Testing Procedures

1. Remix the blood sample immediately prior to centrifugation by gently inverting the tube 4-6 times. Centrifuge tube/blood sample at room temperature (18-25°C) in a swinging bucket centrifuge rotor for 25 minutes at 1500-800 RCF (Relative Centrifugal Force) with **NO BRAKE**.
2. Cryotube preparation: For each CPT tube, prepare 1 cryotube for plasma and 2 cryotubes for

PBMC collection. Label each tube.

3. After centrifugation, PBMCs will be a cloudy layer just below the plasma layer. Collect 1mL of plasma with a 1000 μ L pipette and transfer to a labeled cryotube. Collect PBMC layer (approximately between 1-3mL) with a 1000 μ L pipette and transfer to a 50mL conical centrifuge tube. (Collection of cells immediately following centrifugation will yield best results).
4. Cell washing: Add sterile 1X PBS to bring volume to 50mL. Cap the tube. Mix cells by inverting 5 times. Take 10 μ L of resuspended cells for cell counting. Centrifuge the 50mL tube at 4°C in a swinging bucket rotor for 5 minutes at 300 RCF (Relative Centrifugal Force).
5. After centrifugation aspirate supernatant and gently tap tube with finger to loosen the pellet.
6. Resuspend cell pellet by adding 1.5mL cryomedium (10% DMSO in FBS) for each cryotube that you are going to freeze.
7. Transfer 1.5mL of resuspended cells to each labeled cryotube.
8. Put cryotubes into a freezing container containing isopropanol (250mL) at room temperature and then store the freezing container in a -80°C freezer. After 24-48 hours, transfer the cryotubes from the -80°C freezer to a liquid nitrogen freezer. **CAUTION:** Transfer your samples from the -80°C freezer to the liquid nitrogen tank as quickly as possible to prevent cell damage.

Note: After processing for viable freezing, the samples are frozen at -80°C and then in liquid nitrogen and stored in liquid nitrogen until use. Each patient sample is assigned a unique 2D barcode identifier. Flow cytometric analysis is performed as a batch analysis due to the necessity of running each patient's pre-therapy and post-therapy samples contemporaneously, and to minimize variability due to different runs, reagents, and ambient conditions.

C. References

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III. Plasma Angiome

A. Overview

Plasma samples will be analyzed by multiplex ELISA assays for plasma-based biomarkers utilizing the Aushon Cirascan Imaging System. The Aushon Cirascan Imaging System is used specifically for the imaging and analysis of chemiluminescent protein arrays in a 96-well plate. The protein arrays are created by spotting up to 16 different capture antibodies per well in each well of the 96-well plate. The advantage of this system is that multiple target proteins of interest can be analyzed at the same time reducing the amount of sample required for analysis. In brief, a small volume of sample and/or standard is added to each well of the 96-well plate resulting in the capture of the target proteins by the arrayed antibodies. Biotinylated antibodies are then added that specifically bind the captured target proteins. Streptavidin conjugated to HRP (horseradish peroxidase) is then added followed by a chemiluminescent substrate. Imaging of the plate is performed using Aushon Cirascan Imaging System. Protein concentrations in the samples are quantified by comparing the intensity of the spots in the unknown wells to standard curves.

B. Laboratory Testing Procedures

Dilution of Patient Samples:

- 1) Add dilution buffer to staging plate followed by patient sample.
- 2) Dilution strategies vary depending on target analyte.

Reconstitution of Standards:

- 1) Add proper volume of Sample Diluent to each standard vial; let stand for 1-2 minutes followed by gentle inversion.
- 2) Ensure lyophilized standard on sides of tube and cap are added to solution.
- 3) Allow standards to sit at room temperature while preparing standard serial dilutions.

Serial Dilution of Standards:

- 1) Perform serial dilutions for 7 standards and one blank as per Aushon instructions.
- 2) Pipette 150-200ul of each standard to the pre-designated area on the staging plate.

Loading Samples onto Ciraplex Plates:

- 1) Once staging plates have been prepared; remove Ciraplex plates from package and label accordingly.
- 2) Add 50ul of each patient sample and standard, in duplicate, onto Ciraplex Plate using a Rainin multi-channel manual pipetman without changing tips between replicates.
- 3) Cover plates using adhesive plate sealer and incubate 2 hour at room temperature while shaking at setting 6 (Barnstead 4625).

Washing plates:

- 1) Washing plates is performed using the BioTek ELx405 plate washer. (See *BioTek Plate Washer Instructions* below)
- 2) Use the Vacuboy Multi-Channel to remove all wash buffer followed by 20 second spin in Labnet MPS1000 plate spinner.

Biotinylated Antibody Reagent Addition:

- 1) Add the entire bottle of biotinylated antibody to a 50ml reagent reservoir.
- 2) Pipette 50ul of biotinylated antibody reagent to each well using a Rainin multi-channel manual pipetman. Do not change tips during the addition of this reagent.
- 3) Cover plates using adhesive plate sealer and incubate 30 minutes at room temperature while shaking at setting 6 (Barnstead 4625).
- 4) After 30 minutes, wash plates as described above.

Streptavidin-HRP Reagent Addition:

- 1) Add the entire bottle of streptavidin-HRP to a fresh 50ml reagent reservoir.
- 2) Pipette 50ul of streptavidin-HRP reagent to each well using a Rainin multi-channel manual pipetman. Do not change tips during the addition of this reagent
- 3) Cover plates using adhesive plate sealer and incubate 30 minutes at room temperature while shaking at setting 6 (Barnstead 4625).
- 4) After 30 minutes, wash plates as described above.

Signal Detection:

- 1) Once plates have been washed and all wash buffer and bubbles have been removed; mix 4.0ml Super Signal and 4.0ml Peroxidase solutions in a 15ml conical tube and mix by inverting five times.
- 2) Pipette 50ul of detection solution using a reagent reservoir and multi-channel pipetman.
- 3) Protect from light and incubate 2 minutes at room temperature while shaking at setting 2 (Barnstead 4625).
- 4) Read immediately on the Aushon Cirascan Instrument.

C. References

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IV. Olaparib and Cediranib PK

Samples for determination of cediranib and olaparib concentrations in plasma will be analyzed by Covance using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Results will be only reported for samples shipped within a timeframe for which the stability of cediranib and olaparib in the samples has been validated and shown to be acceptable.

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report. Anonymized samples will be retained for no more than 5 years after the Clinical Study Report is finalized.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

V. BRCA1 Promoter Methylation

A. Overview

For the BRCA1 promoter methylation assay, genomic DNA samples will be bisulfite treated for hydrolytic deamination of nonmethylated cytosines to uracils, whereas methylated cytosines are resistant to conversion. The degree of methylation is calculated as allele frequency: $\text{methylation \%} = [\text{peak height methylated} / (\text{peak height methylated} + \text{peak height non-methylated})] * 100$ using the allele quantification functionality of the PyroMark Q24 software and can be exported to be further treated with statistical or graphical software. Thresholds are established based on an average methylation value across 11 CpG sites and test interpretation is reported as positive if the mean methylation is between 10% and 99% and negative if the mean methylation is less than 10%. These cut-offs were chosen based on multiple experiments where non-methylated samples were routinely measured at <10% and generally ~5% and methylated samples were routinely >40%.

BRCA1 promoter methylation is found in ~10% of high-grade serous ovarian cancers by The Cancer Genome Atlas (TCGA) and others. BRCA1 promoter methylation is a likely candidate to modify response to PARP inhibitor treatment. This assay has received CLIA approval in New York State and can be performed as an integrated biomarker or an exploratory biomarker. The methods are summarized briefly below.

Realizing the important participation of DNA methylation in the pathogenesis of cancer and other diseases, a variety of techniques for the study of DNA methylation have been developed in the last few years. Pyrosequencing has the ability for the simultaneous analysis and quantification of the degree of methylation at several CpG positions in close proximity. The Pyrosequencing technology is based on the luminometric detection of pyrophosphate that is released on nucleotide incorporation and converted into a light signal by a cascade consisting of four enzymes. One of its major strengths is the quantitative nature of the results. The bioluminometric response is linear ($R^2 > 0.99$) for the sequential addition of up to five identical nucleotides (C, G, and T) or three dATPs. Pyrosequencing is ideally suited for DNA methylation analysis after bisulfite treatment of DNA because it combines the ability of direct quantitative sequencing, reproducibility, speed, and ease-of-use. In addition, it allows the interrogation of multiple consecutive CpG sites.

The assay was validated through the use of 15 samples previously tested through TCGA project. All of our results obtained by pyrosequencing analysis matched with the previous results. Intra-assay reproducibility was confirmed by obtaining concordant results in six samples tested in triplicate in the same run. Inter-assay reproducibility was confirmed by obtaining concordant results in six samples assayed on multiple dates. To determine the sensitivity of this assay, we performed a dilution series experiment using seven mixtures of methylated DNA (Millipore positive control) and unmethylated genomic DNA (100%, 50%, 25%, 12.5%, 6.25%, 3.125%, and 1.56%). Overall, there was a high degree of correlation ($r > 0.994$). This data indicate that this Pyrosequencing assay always gives concordant calls for the methylation status when a 10% threshold to declare methylation is used. The sensitivity of this assay is 6%. The analytical metrics demonstrate that the assay had very high inter- and intra-assay reproducibility. The bioluminometric response of pyrosequencing is linear as demonstrated by the high R-squared. The assay has 100% sensitivity and specificity.

B. Laboratory Testing Procedures

One H&E and five unstained formalin-fixed, paraffin-embedded (FFPE) tumor tissue sections (5 μ m thickness) are required for the testing. Adequate tumor should be present in the material submitted for analysis. A section should be confirmed to contain >75% tumor by a surgical pathologist. If the submitted material for analysis contains less than 75% tumor, areas of predominant tumor will be macrodissected using a scalpel to trim away non-neoplastic areas. The quality and quantity of genomic DNA preparation is essential for successful bisulfite conversion. The criteria for 260/280 ratio for DNA quality is set between 1.60 and 2.50. The minimum amount of DNA used for bisulfite treatment is 200 ng.

Genomic DNA samples will be bisulfite treated for hydrolytic deamination of nonmethylated cytosines to uracils, whereas methylated cytosines are resistant to conversion. The degree of methylation is calculated as allele frequency: $\text{methylation \%} = [\text{peak height methylated} / (\text{peak height methylated} + \text{peak height non-methylated})] * 100$ using the allele quantification functionality of the PyroMark Q24 software and can be exported to be further treated with statistical or graphical software. Thresholds are established based on an average methylation value across 11 CpG sites and test interpretation is reported as positive if the mean methylation is between 10% and 99% and negative if the mean methylation is less than 10%.

C. References

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VI. BRCA1 Immunohistochemistry

A. Overview

For BRCA1 immunohistochemistry (IHC), sections will be evaluated for BRCA1 expression with a commercially available monoclonal antibody. Whole sections will be evaluated and will be classified as BRCA1 loss, BRCA1 retained, or BRCA1 equivocal.

B. Laboratory Testing Procedures

For BRCA1 immunohistochemistry (IHC), one whole section will be evaluated with a commercially available monoclonal antibody against BRCA1 (Ab-1) clone MS110 (mAb) from Calbiochem (catalogue number OP92). Whole sections will be used for evaluation. Heat retrieval is performed by steaming with EDTA pH 8 for 30 minutes. This is followed by incubation with the primary antibody for 30 minutes at room temperature (dilution 1:100), followed by incubation with a labeled polymer from Envision TM+ System HRP (Dako) for 30 minutes at room temperature; 3,3'-Diaminobenzidine is used as the counterstain.

The staining pattern will be recorded as BRCA1 loss, BRCA1 retained, or BRCA1 equivocal as follows:

1. BRCA1 loss: Complete absence of staining with presence of positive internal control, or staining in <5% of tumor cells.
2. BRCA1 retained: Staining in >10% of tumor cell nuclei, or moderate-intensity staining in 5% to 10% of tumor nuclei with a moderately intense internal control.
3. BRCA1 equivocal staining: Weak staining in 5% to 10% of tumor cell nuclei, in the presence of moderate to strong internal positive control. Complete absence of staining without positive internal control.

Initially, a semiquantitative assessment for intensity and amount of staining was performed. The stains were then re-evaluated with knowledge of the BRCA status, and a cutoff separating tumors into distinct groups based on genotype was developed. In other words, semiquantitative assessment was used to develop categorical criteria for scoring cases as BRCA1 loss, BRCA1 retained, or BRCA1 equivocal. Two independent and blinded pathologists then validated these

criteria. In our published work (ref 3) we demonstrate that this assay has a PPV of 94%, NPV of 92%, sensitivity of 86% and specificity of 97%.

C. References

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APPENDIX VII: PATIENT DRUG DIARY: OLAPARIB ONLY (11/07/2016)

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

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

OLAPARIB

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

Day	Date	100mg	150mg	AM	PM
1	1/1/15	2	0	8:00	8:00
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
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22					
23					
24					
25					
26					
27					
28					

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

APPENDIX VIII: PATIENT DRUG DIARY CEDIRANIB AND OLAPARIB (11/07/2016)

Today's Date _____ Cycle # _____

Patient Name _____ Patient Study ID _____

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

CEDIRANIB
 Take ____ (number) ____ mg tablets once a day.
Take on an empty stomach 1 hour before taking the morning dose of olaparib.

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

Day	Date	15mg	20mg	AM	Day	Date	100mg	150mg	AM	PM
1	1/1/15	2	0	7:00	1	1/1/15	2	0	8:00	8:00
2					2					
3					3					
4					4					
5					5					
6					6					
7					7					
8					8					
9					9					
10					10					
11					11					
12					12					
13					13					
14					14					
15					15					
16					16					
17					17					
18					18					
19					19					
20					20					
21					21					
22					22					
23					23					
24					24					
25					25					
26					26					
27					27					
28					28					

Patient's Signature: _____

Date: _____

Physician/Nurse/Data Manager's Signature _____

Date _____

APPENDIX IX: PATIENT BLOOD PRESSURE DIARY

Today's Date _____ Cycle # _____

Patient Name _____ Patient Study ID _____

Instructions to the Patient:

1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heart beat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, normal blood pressure is 120/80).
2. Record the date, then record your blood pressure twice each day using a home blood pressure monitor.
 - Each morning while you are resting (not while you are active: dressing, making breakfast, etc.)
 - Each evening at bedtime or while you are relaxing during the evening
3. If you take your blood pressure at other times, record the numbers and time under "Other Readings."
4. If your systolic pressure is greater than 140 **OR** your diastolic blood pressure is greater than 90, please contact your local doctor's office at _____ for instructions.
5. Please bring this form to every clinic visit or appointment.

Day	Date	AM Readings	PM Readings	Other Readings (include time)	Day	Date	AM Readings	PM Readings	Other Readings (include time)
1		/	/		15		/	/	
2		/	/		16		/	/	
3		/	/		17		/	/	
4		/	/		18		/	/	
5		/	/		19		/	/	
6		/	/		20		/	/	
7		/	/		21		/	/	
8		/	/		22		/	/	
9		/	/		23		/	/	
10		/	/		24		/	/	
11		/	/		25		/	/	
12		/	/		26		/	/	
13		/	/		27		/	/	
14		/	/		28		/	/	

Patient's Signature: _____ Date: _____

Physician's office will complete this section:

Date of this clinic visit _____

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

Appendix X: Patient Reported Outcome Supplemental Questions and Plan

Background

Outcomes of the treatment of cancer that are important to clinicians and researchers are not always the same as those that are important to patients. In addition, outcomes of treatment trials do not always point in consistent directions, favoring one treatment over another. In this trial, it is possible that benefits and risks may compete with each other, presenting future patients with treatment choices that would ideally be made with information about these competing benefits and risks. We propose to collect data in this trial that will enable us in future studies to evaluate patients' preferences for the attributes of their treatments, including not only overall survival and progression-free survival, but also the timing and convenience of treatment regimens, symptoms of disease, and side effects of treatments. To accomplish this, we will collect data elements that enable a more accurate and clinically relevant depiction of trial results with regard to not only disease symptoms, but also treatment side effects, function/well-being, and health utility. This information will enable us to examine the association of these outcomes with each other, and with clinical outcomes such as response rate, progression free survival and overall survival.

The regimens being evaluated in this trial differ significantly on many levels. Cytotoxic chemotherapy regimens are typically administered for a shorter time period than biologics, have a different toxicity profile, and do not include ongoing maintenance treatment once a CR is achieved. Out of pocket cost for cytotoxics may be lower due to a more limited treatment period, and the fact that longstanding therapies typically carry lower costs. The data collected in this trial will be extremely useful for subsequent research that can formally elicit patient preferences for one or another treatment based on their personal perspectives on each of the outcomes (RR, PFS, OS, symptoms, side effects, function/well-being, utility). One standard preference elicitation method is conjoint analysis, in which participants evaluate a series of treatment choices with a set of attributes of varying levels. This ultimately allows the assignment of preference weights that could be considered for development of a composite endpoint or development of a patient focused decision tool. Although conjoint analysis is not part of this protocol per se, the data obtained will inform such important work in the future, much the same as is now being done by these same investigators in the area of intraperitoneal versus intravenous chemotherapy. We emphasize that this important work can be done with only a very modest time commitment from patients of 10 minutes per assessment over a 3-year period, and minimal cost to the trial.

Other PRO Measures Beyond Disease Related Symptoms

The DRS-P scale is half of the NFOSI-18 (9 of 18 items). The other 9 items measure Treatment Side Effects (TSE; 5 items) and Function/Well-being (3 items, plus 1 item on worry).

The TSE is a 5-item measure of side effects commonly reported by women receiving treatment for ovarian cancer, selected based on their importance relative to other side effects (Jensen et al, 2011). They include nausea, vomiting, hair loss, skin problems, and a general side effect bother question. We propose to compare groups on the sum of all 5 questions. Because we cannot ask about all possible side effects out of respect for patient time, we also propose to compare groups on the single 'global' side effect bother question. **The broad hypotheses for these comparisons are that patient side effect severity, both for the sum score and the single item global score,**

will be worst on the platinum-based chemotherapy arm, followed by the combination olaparib-cediranib arm, and then the olaparib only arm. That is, each arm will be significantly different from the others, with olaparib alone being least impairing.

Differences in these scores will inform the comparative descriptions of side effect experience for future patient preference studies.

Similarly, the FACT/GOG-Ntx-4 is an efficient 4-item measure of sensory peripheral neuropathy that has been shown to be responsive to platinum and taxane-based chemotherapy. **We hypothesize that the Ntx-4 sum scores will be worse on the platinum-based chemotherapy arm compared to the other two arms which are not expected to differ from one another.**

Differences in these scores will inform the comparative descriptions of side effect experience for future patient preference studies.

The remaining 8 questions in the proposed PRO plan address general function and well-being. (NFOSI-18 F/WB and EQ-5D), and a single question about worry. Consistently, and confirmed in Jensen et al (2011), patients prioritize this area as important and subject to disruption caused by both disease and treatment. We have selected these 8 questions for the following reasons: The 3-item Function/Well-being scale of the NFOSI-18 represents the three most important areas identified by advanced ovarian cancer patients (mobility independence, life enjoyment, and global quality of life). The one-item regarding worry about condition worsening, emerges consistently among patients with advanced cancer as a high priority, and finally, the 5-item EQ-5D is the internationally most widely used measure of health utility.

The EQ5D is a 5 item, preference-based measure of health that can be administered in approximately one minute. The EQ5D utility score is an internationally used metric that also allows validated calculation of quality-adjusted life years for cost-effectiveness analysis. We will use the EQ-5D as the basis for generating a utility score. Our hypotheses are: 1) Patient preference scores (utilities) will be higher (better) during active treatment in the non-cytotoxic therapy arms compared to cytotoxic therapy arms; 2) patient preference scores (utilities) will be lower (worse) in biologic arms than in chemotherapy arm between 6 months and disease progression (the time period when the biologic arms continue treatment but chemotherapy arms are off therapy); and 3) Patient preference scores (utilities) will drop at disease progression.

Statistical Considerations

The focus of the analyses of the NFOSI-18, FACT/GOG-NTX-4 and the EQ-5D is primarily descriptive and involves estimating differences in mean scores, proportions or log odds for each treatment group with confidence intervals.

Scores from the NFOSI-18, EQ5D will be analyzed with mixed models using procedures similar to those described for the NFOSI-DRS.

Missing PRO information

Patient death, noncompliance, missed clinic appointments, and patient low literacy, can cause observations to be missed. One or more of the PRO assessments may be missing for an individual on any occasion. Missing information is troublesome particularly in studies involving repeated patient assessments. The frequency that assessments are missed will be monitored every 6 months throughout the study. Data Coordinators will be working with the Study Team

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and the NRG's Patient Reported Outcome Committee to identify reasons that data are missing and recommending remedial actions when possible.

The PRO instruments used in this study have been translated to several different languages. Women, who are unable to read or have difficulty reading, will not be required to participate in the PRO component of this study, however, a woman may elect to have the items read to her and be assisted in completing the instruments. Interviewers will have been trained to read questions without leading patients toward one response or another, reminding patients as needed that there are no right or wrong answers and that the patient is in the best position to provide the right answer choice.

NCCN-FACT FOSI-18 (Version 2)

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

		Not at all	A little bit	Some-what	Quite a bit	Very much	
D R S- P	GP1	I have a lack of energy.....	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	GP6	I feel ill	0	1	2	3	4
	O3	I have cramps in my stomach area	0	1	2	3	4
	HI7	I feel fatigued.....	0	1	2	3	4
	Cx6	I am bothered by constipation	0	1	2	3	4
	O1	I have swelling in my stomach area	0	1	2	3	4
D R S- E	C3	I have control of my bowels	0	1	2	3	4
	GF5	I am sleeping well.....	0	1	2	3	4
	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
	B5	I am bothered by hair loss	0	1	2	3	4
T S E	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	O2	I have been vomiting	0	1	2	3	4
	BMT15	I am bothered by skin problems	0	1	2	3	4
F W B	BMT5	I am able to get around by myself	0	1	2	3	4
	GF3	I am able to enjoy life.....	0	1	2	3	4
	GF7	I am content with the quality of my life right now.....	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)
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03 March 2010
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FACT/GOG-NTX-4 (Version 4)

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

		Not at all	A little bit	Some- what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands.....	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet.....	0	1	2	3	4
NTX 3	I feel discomfort in my hands.....	0	1	2	3	4
NTX 4	I feel discomfort in my feet.....	0	1	2	3	4

PID: _____
Study ID#: _____

EQ-5D

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today. The following questions are similar to those in the previous section but have slightly different wording.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

Appendix XI: NCI/DCTD Collaborative Agreements Language

Collaborative Agreements Language

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company(ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

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.

Appendix XII: Protocol Monitoring Plan (11/07/2016)

1) Enhanced Centralized Data Monitoring

- a) **Eligibility:** The source records which document the eligibility for the first two individuals enrolled from each site (as identified by a unique NCI identifier) will be reviewed for completeness and consistency with the eligibility criteria, the data reported during the enrollment process and the data reported on the case report forms (CRFs). Documents should be submitted within two weeks of subject enrollment.

In the event that this monitoring identifies unacceptable enrollment procedures or significant deviations from eligibility criteria, then the site will need to submit a corrective action plan within two weeks of being notified of the findings of the centralized monitoring. The source records for the eligibility of treatment for the next individual enrolled to the study from the site should then again be submitted and reviewed. In the event of significant repeated deviations from the protocol, accrual at the site may be suspended per discretion of the overall Study Chair.

The pretreatment documents to be reviewed include:

- i) Pathology Report to document the site, histology and grade of the primary tumor.
 - ii) Baseline imaging reports to confirm the presence of RECIST measurable disease.
 - iii) Verification of platinum-free interval
 - iv) Clinic source documents to verify initial performance status, prior surgery for ovarian cancer, anti-cancer therapies (including agent names, as well as, start and stop dates), and concomitant medications.
 - v) Germline BRCA1/2 Mutation analysis report.
 - vi) Electrocardiogram and ECHO or MUGA reports.
 - vii) Pretreatment hematology and chemistry Reports (including TSH, T4, pregnancy tests and urinalysis).
 - viii) Signed and dated informed consent form
- b) **Drug Accountability, Drug-Dose Compliance and Adverse Events:** The source records and adverse events (AEs) during *the first two cycles* of treatment for the first two individuals enrolled from each site will be reviewed for compliance with the protocol, completeness and consistency with the data reported on the case report forms, and drug accountability records. The documents listed below should be submitted at two time-points: (1) within two weeks of beginning the second cycle of treatment (for records and AEs during the first cycle of treatment), and (2) within two weeks of beginning the third cycle of treatment (for records and AEs during the second cycle of treatment).

In the event that this monitoring identifies unacceptable procedures or significant deviations from protocol procedures, then the site will need to submit a corrective action plan within two weeks. The source records for the first two cycles of treatment for the next individual enrolled to the study from the site should then again be submitted and

reviewed. In the event of significant repeated deviations from the protocol, accrual at the site may be suspended per discretion of the overall Study Chair.

The documents to be reviewed include:

- i) Study drug orders treatment dose calculations and administration records.
- ii) Reports from protocol-directed laboratory studies.
- iii) Reports from any additional tests performed to document an adverse event.
- iv) Patient drug diaries and pill counts.
- v) Pharmacy drug accountability records.
- vi) Summaries of hospital admissions and discharge for hospitalizations.
- vii) Summaries of surgical procedures performed.

2) Documentation of Disease Progression

All imaging studies that are used by the treating physician to evaluate the disease status for each and every enrolled patient from just prior to initiating study treatment up until progression or death, whichever occurs first, will be prospectively collected and stored electronically. All collected images will be appropriate de-identified. If it is deemed appropriate, then these images will be available for trained independent radiologists to review in a standardized fashion. Also, in the event that progression is based on the interpretation of a pathologic finding, a copy of the pathology report will be collected and stored.

3) On-Site Auditing

An on-site audit will be conducted at any site where a patient was enrolled within two years of the anticipated date when the study is expected to mature for the final analysis

4) Protocol Master File

A Protocol Master File will be maintained centrally throughout the study which will include regulatory documents.

a) The study-specific documents:

- i) The active-version of the study document (including the informed consent document).
- ii) A list of study amendments.
- iii) The active-version of the protocol and informed consent document prior to each study amendment.

b) The institutional-specific documents:

- i) Documentation of the Principal Investigator's, co-investigators' and clinical research associates' GCP training.
- ii) Documentation of the Principal Investigator's, co-investigators' and the clinical research associates' protocol-specific training.

5) Submission of Documentation

Regulatory documents, including 1572 Forms, and Financial Disclosure Forms, as well as instructions for submitting these forms, are available from

http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the **CTEP Investigator Registration Help Desk** by email at pmbregpend@ctep.nci.nih.gov.

Regulatory documents should be submitted to the CTSU Regulatory Office, as per Section 8.1.2.4 in the main protocol.

The Case Report Forms (CRFs) and any required source documentation that will be used for enhanced centralized data monitoring will be submitted through the Medidata/RAVE electronic data capture (EDC) system.

While the images (e.g. CT scans, X-rays) for documenting progression will not be stored in Medidata/RAVE, special CRFs in EDC system will be used to facilitate the process of uploading files to the image storage system and collecting the image metadata.

APPENDIX XIII: NRG General Guidelines (11/07/2016)

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be scheduled).

For patients on Arms II or III of this protocol, the “Day 1” visit of the cycle may take place within a “7 day window of the protocol-defined date” for major life events. Sufficient drug to encompass this window should be dispensed to the patient at the preceding visit if needed. Patients on Arms II and III of this protocol who have their visit delayed should have their next visit scheduled as per their original schedule (e.g., a patient whose Cycle 2 “Day 1” visit was delayed by a week should have their Cycle 3 “Day 1” visit 3 weeks after the delayed Cycle 2 “Day 1” visit occurs, not 4 weeks after the delayed visit).

- For patients on Arm I of the protocol, it will be acceptable for individual chemotherapy doses to be delivered within a “24 hour window before and after the protocol-defined date” for “Day 1” treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through Monday (day 3 past due).
- For patients on Arms II and III of the protocol, it will be acceptable for the “Day 1” visit of each cycle to take place within a “72 hour window before and after the protocol-defined date.”
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a “24-hour window,” for example; “Day 8 chemotherapy” can be delivered on Day 7, Day 8, or Day 9 and “Day 15 chemotherapy” can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be “rounded” according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose)
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for <10% weight changes.

APPENDIX XIV: DIAGNOSTIC IMAGE COLLECTION SUMMARY (11/07/2016)

Accrual: 450 subjects

Activation Date: February 4, 2016

Duration of Trial (mos): 60 mos.

Approx. scan collection per subject:

- a. ~6 scans per year up to 12 months or until progression
 - b. After 12 months: ~4 scans per year until progression
1. CT scan or MRI performed once every 9 weeks (+/- 7 days), and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Imaging assessments can be discontinued if disease progression.
 2. If a patient discontinues study treatment for any reason other than progression, imaging studies should continue every 9 weeks (+/- 7 days) until progression.
 3. After 1 years of protocol therapy or follow-up (measured from approximately cycle 1, day 1), imaging studies will be conducted every 12 weeks.

TRIAD Digital Image Submission:

TRIAD is the secure electronic image upload application utilized for IROC Services of this trial. TRIAD de-identifies and validates the images as they are transferred.

1. TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Philadelphia DI. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

- Site staff who submits images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account.
- To submit images, the site user must be on the site's affiliating rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

2. TRIAD Installations:

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation. Documentation can be found by following this link

<https://triadinstall.acr.org/triadclient/>

Questions regarding image submissions should be directed to:

IROCPHILA-DI@acr.org.

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Questions about TRIAD should be directed to:
<http://triadhelp.acr.org/ClinicalTrials.aspx>

Tech Support is available from Monday to Friday between 8am - 5pm EST.

Contact By Phone:

703.390.9858

Contact By Email:

Triad-Support@acr.org

APPENDIX XV: Japan (11/07/2016) (07/31/2017)

Background and Purpose

The primary endpoint of NRG-GY004 trial is to evaluate the efficacy and safety of a regimen that combines cediranib and olaparib in women with platinum sensitive recurrent ovarian cancer. Although, phase I studies of single agent olaparib¹ or cediranib² in the Japanese population showed similar toxicity profiles and the same MTDs as the Caucasian population, the safety information of the combination of olaparib and cediranib in Japanese women is lacking. Safety evaluation of cediranib in the Japanese patients was tested in combination with mFOLFOX6³ or S-1⁴. Recommended dose of cediranib was 20-30 mg with mFOLFOX6 and 20 mg with S-1.

Cediranib is a small molecule tyrosine kinase inhibitor. In a clinical trial using pazopanib, a multiple kinase inhibitor for c-KIT, FGFR, PDGFR, and VEGFR, as maintenance therapy after first line chemotherapy for ovarian cancer, significant prolongation of PFS was observed. However, adverse events and dose reductions occurred significantly more frequently in an East Asian population and an improvement in the prognosis was not observed⁵.

This has raised a concern that a similar ethnic difference may occur in the GY004 trial. Therefore, GY004 will include a small Japanese run-in cohort to assess the toxicity profile and the frequency of unexpected toxicities in the Japanese population when the olaparib and cediranib combination is administered.

Methods

Eligibility

Eligibility and ineligibility of the enrollment in this cohort is exactly the same as main protocol, section 3.1 and 3.2.

Protocol Therapy

The treatment will be the same as Arm III of the main protocol, which is the combination of olaparib and cediranib.

Olaparib 200mg in tablet formulation orally twice daily continuous dosing

Cediranib 30mg in tablet formulation orally once daily.

One cycle will be considered 28 days.

Patients will remain on treatment until disease progression.

Patients will be required to maintain medication and blood pressure diaries (found in Appendix VIII and IX).

A blood pressure cuff will be provided to patients randomized to Arm III.

Evaluation of Toxicity

Toxicities will be evaluated based on CTCAE during the 1st Cycle of the protocol therapy.

For the purposes of this sub-study a dose-limiting toxicity (DLT) will be any of the following adverse events occurring any time between the initiation of the first cycle of treatment and initiation of the second cycle of treatment

- Non-Hematologic Toxicity
 - Unanticipated Serious Adverse Events (SAEs)
 - Hypertension or diarrhea SAEs that occur in the setting of optimal maximal medical management, as detailed in Section 6.2.2.1 and 6.2.2.2 of the main protocol
- Hematologic Toxicity
 - Grade 4 neutropenia of ≥ 4 days duration
 - Grade 4 neutropenia of any duration with fever or documented infection
 - All other hematologic toxicities of Grade 4
- Inability to take 75% or more of the planned dose in Cycle 1 due to treatment-related AEs

Management and dose modifications associated with the above adverse events are outlined in Section 6 of the main protocol.

Accrual During the Run-in Phase

A maximum of 12 patients who initiate the first cycle of treatment will be enrolled in this run-in cohort. At the time when first 6 patients enrolled, further enrollment will be interrupted, and the toxicities will be evaluated.

If 3 or more patients experience a DLT, then the regimen will be considered poorly tolerated by Japanese patients and accrual from Japan will be stopped.

Otherwise, an additional 6 Japanese patients will be enrolled and treated.

If more than 4 patients experience a DLT among these 12 patients, then the regimen will be considered poorly tolerated by Japanese patients and no patients from Japan will be enrolled onto the randomized phase 3 study.

Statistical Considerations

Using the criteria mentioned above, if the true probability of a DLT is 0.20, then there is a 77% chance of declaring the regimen tolerable. However, if the true probability of a DLT is 0.40, then there is a 79% chance of declaring the regimen poorly tolerated and a 45% chance of coming to this conclusion after only the first stage of accrual.

Laboratory evaluation

Bicarbonate is not required for patients enrolled in Japan for the serum chemistry assessments as outlined in Tables 4.1 and 4.2.

Germline BRCA mutation test

Germline BRCA mutation test is not required for run-in cohort patients.

Collection of Biospecimens

Collection of Biospecimen is not required except for PK sampling.

PK sampling should be done according to the section 11.2.1.1 Integrated Biomarker Specimen Requirements of main protocol.

References

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