NRG ONCOLOGY

Advancing Research. Improving Lives.™

SUMMARY OF CHANGES

For Protocol Amendment #15 to: NRG-GY005
NCI Protocol #: NRG-GY005
Local Protocol #: NRG-GY005
NCI Version Date: 07/27/2023

This amendment is being submitted in response to an RRA from Dr. S. Percy Ivy (ivyp@ctep.nci.nih.gov).

#	Section	Comments
1.	Title Pages	• NCI Version Date is now July 27, 2023.
2.	7.3.2	Revised Olaparib CAEPR (Version 2.6, June 5, 2023) inserted into protocol Added New Risk: • Rare but Serious: Vascular disorders - Other (venous thromboembolism)
3.	ICD	See informed consent for additional changes.

NRG-GY005

(ClinicalTrials.gov NCT # 02502266)

A Randomized Phase II/III study of the combination of **C**ediranib and **O**laparib compared to **C**ediranib or **O**laparib alone, or **S**tandard of care chemotherapy in women with recurrent platinum-resistant or -refractory ovarian, fallopian tube, or primary peritoneal cancer (COCOS)

NCI Version Date: July 27, 2023

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

Lead Organization: NRG / NRG Oncology

Participating Organizations

ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG
CCTG / Canadian Cancer Trials Group

Coordinating Center:
NRG Oncology
Four Penn Center, 1600 JFK Blvd., Suite 1020
Philadelphia, PA 19103

Study Team

Study Chair	**Study Co-Chair**
Jung-Min Lee M.D.	Angeles Alvarez Secord M.D., MHSc.
Center for Cancer Research	Duke University Medical Center
National Cancer Institute	Room 25172 Morris Bldg.
10 Center Drive, Bldg 10, Rm 12N226	DUMC Box 3079
Bethesda, MD 20892	Durham, NC 27710
240-760-6128/ FAX: 240-541-4547	919-684-3765/FAX: 919-684-8719
leej6@mail.nih.gov	Secor002@mc.duke.edu
Translational Science Co-Chair	**Translational Scientist**
Michael Birrer, MD, PhD	Heather A Lankes, PhD, MPH
University of Alabama at Birmingham	NRG Oncology
1824 Sixth Avenue South	Four Penn Ctr, 1600 JFK Blvd, Ste 1020
WTI 202	Philadelphia, PA 19103
Birmingham, AL 35294	LankesH@NRGOncology.org
205-934-5077	
mbirrer@uab.org	

Correlative Scientists	**Statistician**
Elizabeth Swisher, MD	Austin Miller, PhD
University of Washington	NRG SDMC-Buffalo Office
	Roswell Park Cancer Institute
Andrew Nixon, PhD, MBA	Elm and Carlton Streets
Duke University	Buffalo, NY 14263-0001
	716-845-5702/ FAX: 716-845-8393
William Rodgers,PhD, MD **(06-AUG-2021)**	millera@nrgoncology.org
New York Presbyterian	
Data Manager (06-AUG-2021)	**Research Nurse**
Sandra Dascomb	Nicole Houston, RN
NRG SDMC-Buffalo Office	Center for Cancer Research
Roswell Park Cancer Institute	National Cancer Institute
Elm and Carlton Streets	10 Center Drive, Bldg 10, Rm 12N226
Buffalo, NY 14263-0001	240-760-6127/ FAX: 240-541-4547
716-845-5702/FAX: 716-845-8393	houstonnd@mail.nih.gov
dascombs@nrgoncology.org	
	Quality of Life Chair
Protocol Administrator (22-SEP-2022)	Lari Wenzel, PhD
Kathryn Miller	lwenzel@uci.edu
NRG Oncology	
Four Penn Ctr, 1600 JFK Blvd, Ste 1020	**Comparative Effectiveness Research Chair**
Philadelphia, PA 19103	Laura Havrilesky, MD
215-854-0770/FAX: 215-854-0716	havri001@mc.duke.edu
millerk@nrgoncology.org	

Protocol Agent

Agent	**Supply**	**NSC #**	**IND #**	**IND Sponsor**
Cediranib	CTEP	747856		DCTD, NCI
Olaparib	CTEP	732208		DCTD, NCI

Participating Sites

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

Document History

	Version/Update Date	**Broadcast Date**
Amendment 15	**07/27/2023**	
Amendment 14	**09/22/2022**	
Amendment 13	08/27/2021	
Amendment 12	08/06/2021	
Amendment 11	09/06/2019	
Amendment 10	07/16/2019	

Amendment 9	05/24/2019	
Amendment 8	01/15/2019	
Amendment 7	10/12/2018	
Amendment 6	08/14/2018	
Amendment 5	07/13/2018	
Amendment 4	10/02/2017	
Amendment 3	03/28/2017	04/24/2017
Amendment 2	01/03/2017	01/17/2017
Amendment 1	09/29/2016	12/05/2016
Activation	11/17/2015	02/04/2016

NRG-GY005

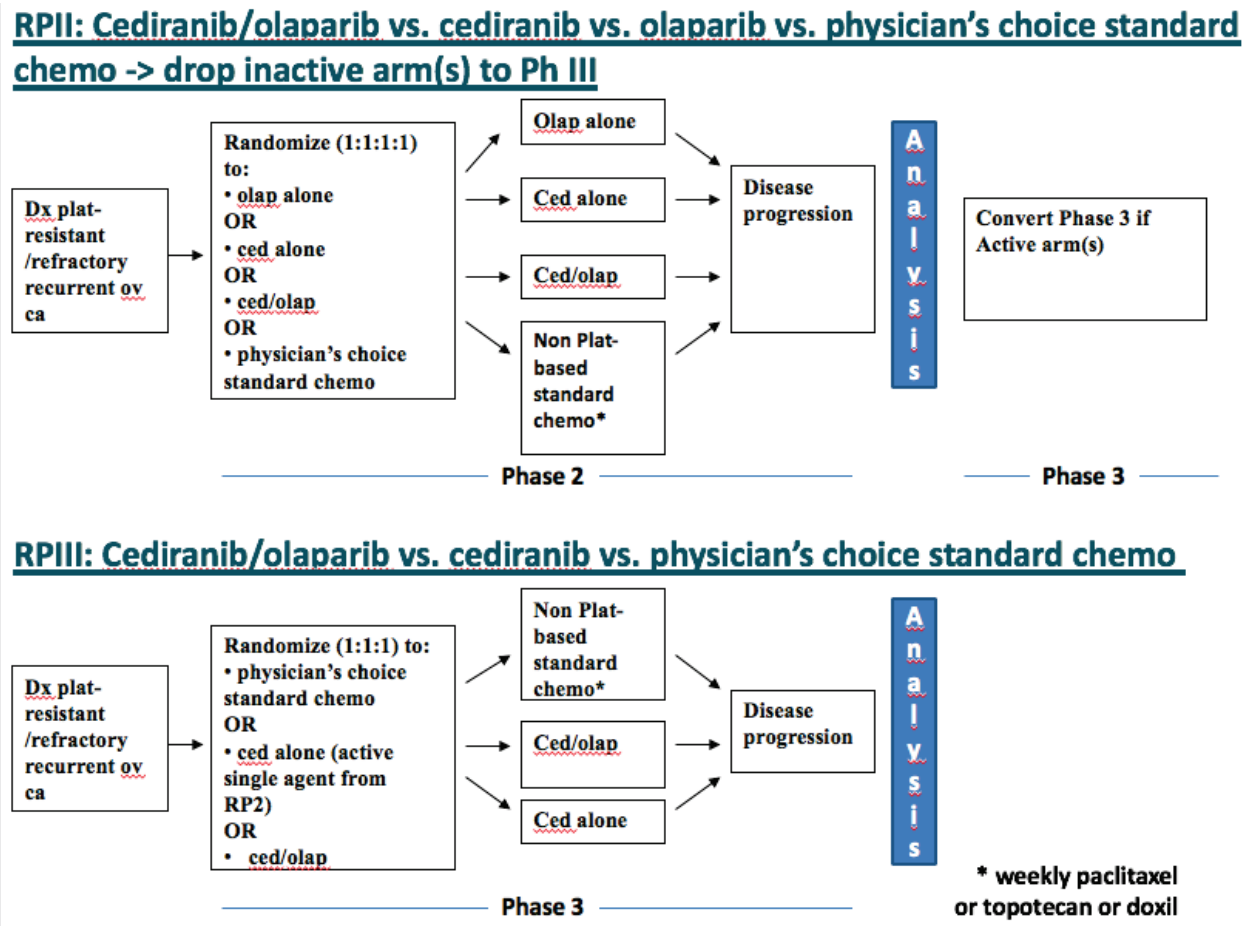
A Randomized Phase II/III study of the combination of **C**ediranib and **O**laparib compared to **C**ediranib or **O**laparib alone, or **S**tandard of care chemotherapy in women with recurrent platinum-resistant or -refractory ovarian, fallopian tube, or primary peritoneal cancer (COCOS)

NCI Version Date: July 27, 2023

Lead Organization: NRG / NRG Oncology

CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
CTSU Regulatory Office 1818 Market Street, Suite 3000 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	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_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
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.		
For clinical questions (i.e. patient eligibility or treatment-related) *Contact the Study PI of the Lead Protocol Organization*		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

SCHEMA



Phase II accrual was suspended on June 16, 2017. At the interim analysis in July 2018, the Data Monitoring Committee voted to drop the single-agent olaparib arm. The Phase III trial will be continued with 3 arms: standard chemotherapy, cediranib+olaparib, and cediranib alone. Phase II patients treated on these three arms will be included in the Phase III trial. References to the single-agent olaparib arm have been retained in the protocol for context.

TABLE OF CONTENTS

1.0 OBJECTIVES

Phase II study:

1.1 Primary Objective

1.1.1 To assess the efficacy and identify (in)active arm(s) of the combination of cediranib and olaparib, cediranib alone, olaparib alone, and physician's choice standard of care chemotherapy, as measured by progression free survival (PFS) in the setting of recurrent platinum-resistant or-refractory ovarian, primary peritoneal or fallopian tube cancer.

1.2 Secondary Objectives

1.2.1 To assess the efficacy of the combination of cediranib and olaparib, cediranib alone, olaparib alone, and physician's choice standard of care chemotherapy, as measured by objective response rate (ORR: partial or complete response) by RECIST 1.1 criteria, in the setting of recurrent platinum-resistant or-refractory ovarian, primary peritoneal or fallopian tube cancer.

1.2.2 To assess safety endpoints, as measured by frequency and severity of adverse events by Common Terminology Criteria for Adverse Events (CTCAE).

1.3 Objectives with Integrated Biomarkers

1.3.1 To assess correlation of homologous recombination deficiency (HRD) status, as assessed via BROCA-HR assay with response, as measured by PFS and ORR.

1.3.2 To evaluate the prognostic and predictive role of circulating endothelial cells (CEC) on comparative effectiveness of targeted therapies and reference chemotherapy.

1.3.3 To evaluate quality of life data compliance, as measured by the 9-item Disease Related Symptoms (DRS-P) subscale of the NCCN-FACT Ovarian Symptom Index (NFOSI) for utilization and analysis in the Phase III study. Additional QOL/PRO items will be collected, as proposed in 1.8.2.

1.4 Exploratory Objectives

1.4.1 To assess exploratory biomarkers of potential HRD, including genomic scarring, BRCA1 methylation, BRCA1 protein expression, and mutations in NHEJ, and other genes that might modify HRD.

1.4.2 To evaluate the prognostic and predictive role of angiogenic biomarkers, as assessed by the Duke plasma angiome.

Phase III study:

1.5 Primary Objective

1.5.1 To assess the efficacy of the combination of cediranib and olaparib, and cediranib monotherapy, as measured by overall survival (OS) and PFS, as compared to physician's choice standard of care chemotherapy in women with recurrent platinum-resistant or-refractory ovarian, primary peritoneal or fallopian tube cancer.

1.6 Secondary Objectives

1.6.1 To assess the efficacy of the combination of cediranib and olaparib, and cediranib monotherapy, as measured by ORR as compared to physician's choice standard of care chemotherapy in the setting of recurrent platinum-resistant or-refractory ovarian, primary peritoneal or fallopian tube cancer.

1.6.2. To assess safety endpoints, as measured by frequency and severity of adverse events by Common Terminology Criteria for Adverse Events (CTCAE).

1.7 Objectives with Integrated Biomarkers

1.7.1 To assess correlation of HRD status, as assessed via BROCA-HR assay with response, as measured by OS, PFS and ORR.

1.7.2 To evaluate the prognostic and predictive role of circulating endothelial cells (CEC) on comparative effectiveness of targeted therapies and reference chemotherapy.

1.7.3 To 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 cediranib and cediranib/olaparib combination, compared to standard chemotherapy, in the setting of recurrent platinum-resistant or-refractory ovarian, primary peritoneal or fallopian tube cancer.

1.8 Exploratory Objectives

1.8.1 To assess exploratory biomarkers of potential HRD, including genomic scarring, BRCA1 methylation, BRCA1 protein expression, and mutations in NHEJ, and other genes that might modify HRD.

1.8.2 To evaluate the prognostic and predictive role of angiogenic biomarkers, as assessed by the Duke plasma angiome

1.8.3 To 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 cediranib and cediranib/olaparib combination, compared to standard chemotherapy, in the setting of recurrent platinum-resistant or-refractory ovarian, primary peritoneal or fallopian tube cancer.

2.0 BACKGROUND

2.1 Platinum-resistant/refractory ovarian cancer

Most patients with epithelial ovarian cancer present with advanced disease at diagnosis (Cannistra et al., 2004; Parmar et al., 2003). The combination of a platinum drug with a taxane is the standard of care for the systemic first-line treatment after primary cytoreductive surgery (du Bois et al., 2003; McGuire et al., 1996). This combination results in response rate (RR)s of ~70% in patients with suboptimally-debulked disease, and of ~ 80% in optimally cytoreduced patients (Ozols et al., 2003; Ledermann et al., 2010). However, disease recurrence is common in this patient population and most patients with recurrent ovarian cancer eventually develop platinum resistant disease (defined as disease recurring within 6 months after the last receipt of platinum-based chemotherapy) (Markman et al., 2000). RRs and duration of response to second-line chemotherapy for patients with recurrent platinum-resistant disease are significantly lower than those with platinum-sensitive disease. In women with platinum-resistant disease, RRs range from 10%-25% and duration of response is typically less than 6 months to chemotherapeutic agents, such as pegylated liposomal doxorubicin (PLD), topotecan, taxanes, etoposide, and gemcitabine. In comparison, the RRs are usually >30% and/or duration of response >8 months in women with platinum-sensitive disease (Markman et al., 2000; Matsuo et al, 2010). Overall, relapse therapy is not curative and is administered with palliative intent only. Thus, there is an urgent need for the development of alternative therapies given the poor response of recurrent disease to traditional cytotoxic agents. Two potential therapeutic targets are DNA damage repair and angiogenesis pathways.

2.2 Activity of olaparib and cediranib as single agents and in combination with chemotherapies

Olaparib (Lynparza™) is a FDA-approved oral PARP-inhibitor for the treatment of advanced ovarian cancer with germline BRCA mutation (gBRCAm). Olaparib has demonstrated activity both in women with gBRCAm-related and BRCA-wild type (BRCAwt) ovarian cancer, with reported RRs of ~40% in gBRCAm carriers and 24% in non-gBRCAm carriers (Ledermann et al., 2014; Lee et al., 2014). A phase II study comparing olaparib capsules monotherapy to PLD therapy in women with gBRCAm-related ovarian cancer, recurrent <12 months after last receipt of platinum-therapy, found no advantage to olaparib therapy in this setting, due to newly identified increased susceptibility of mutation carriers to PLD (Kaye et al., 2012). Data also suggest that olaparib capsules monotherapy response is associated with platinum-sensitivity; lower RRs were noted in platinum-resistant disease (Fong et al., 2010; Gelmon et al., 2011). Additionally, a phase I study of olaparib in capsule formulation and carboplatin in gBRCAm-associated recurrent ovarian cancer (NCT01445418) yielded a RR of 25% (5 of 20) with a median PFS of 13 months (6-40+ months), in platinum-resistant and platinum-refractory patients

(Lee et al., 2014). These findings support the hypothesis that tumors with DNA repair defects may be sensitive to PARP inhibitor-based therapy even after acquiring platinum resistance.

Cediranib is a small-molecule kinase inhibitor of VEGFR-1, -2, -3, with demonstrated activity in both platinum-sensitive and platinum-resistant ovarian cancers (Matulonis et al., 2009). A phase II study of cediranib (30 mg daily) for recurrent ovarian or peritoneal or fallopian tube cancer demonstrated a clinical benefit rate (CBR, defined as CR, PR, SD ≥ 16 weeks, or CA-125 non-progression > 16 weeks), of 30% (further detailed in Section 3.3). Overall, eight patients (17%) had a PR, and six patients (13%) had SD (Matulonis et al., 2009). The ICON6 study demonstrated that the combination of cediranib together with platinum-based chemotherapy and followed by cediranib maintenance, could extend PFS and OS, in women with platinum-sensitive ovarian cancer (Ledermann et al., 2013; Fig 1).

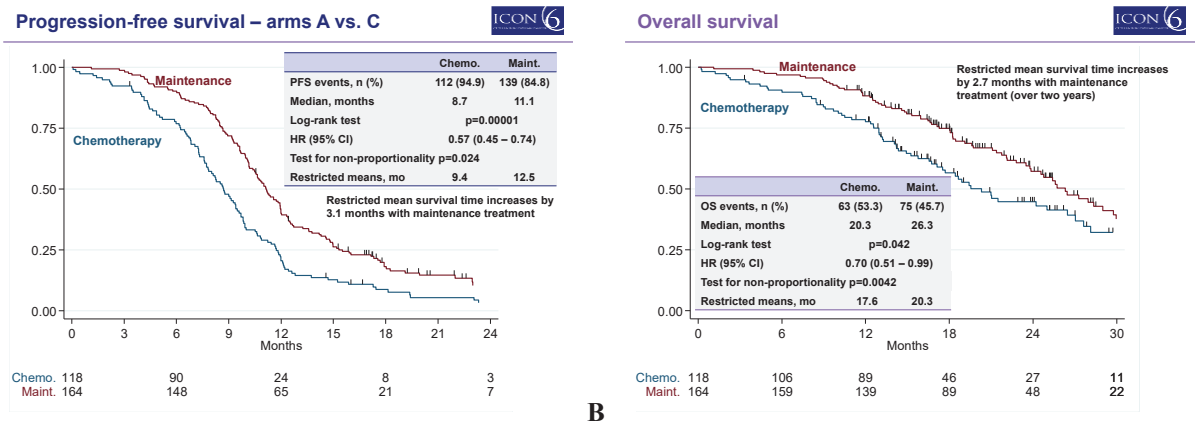
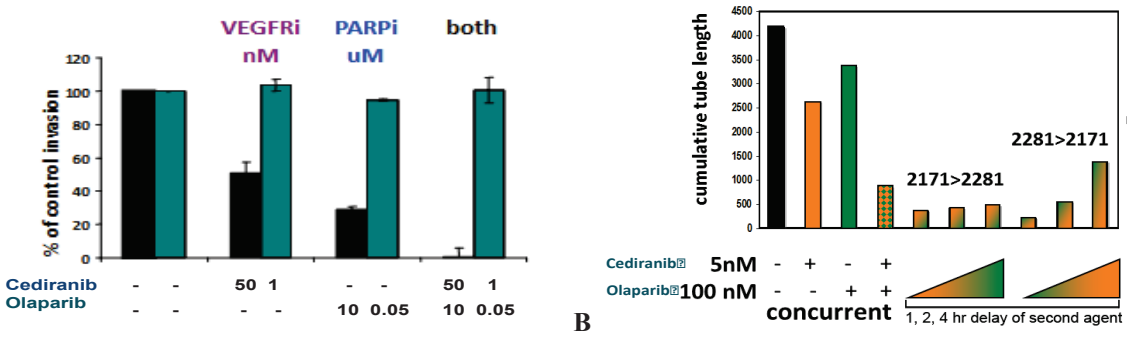


Figure 1. Kaplan-Meier survival curve: cediranib plus platinum-based chemotherapy followed by maintenance cediranib provides a statistically significant benefit in PFS (A) and OS (B), compared to chemotherapy alone in recurrent ovarian cancer.

2.3 Activity of the combination of olaparib and cediranib in recurrent ovarian cancer

Kim and colleagues in unpublished studies found that the combination of cediranib and olaparib inhibited invasion of ovarian cancer cells (Fig 2A). Invasion was significantly decreased in pretreated ovarian cancer cell lines, CAOV3 and OVCAR8, exposed to concentrations attainable in patients, 50 nM cediranib or 10 uM olaparib, or a combination of both drugs ($p<0.0001$ for all treatments). Additional data showed that the combination of cediranib and olaparib inhibited in vitro endothelial vascular tube formation on Matrigel at concentrations well below those clinically attainable in patients (Fig 2B). Tube length was significantly reduced when endothelial cells were exposed to 5 nM cediranib or 100 nM olaparib ($p<0.003$ and $p<0.001$, respectively). The combination of olaparib and cediranib resulted in greater inhibition of tube formation than monotherapy ($p<0.0001$). These preclinical findings provide further rationale for clinical investigation of this new combination strategy for recurrent ovarian cancer.



A. B

Figure 2. Cediranib and olaparib, with clinically relevant selected doses, combine effectively to (A) reduce invasion and (B) reduce microvascular cell tube organization as compared to either agent alone.

There was unexpected response signal in platinum-resistant ovarian cancer from the phase I study of the combination of cediranib and olaparib in capsule formulation (Liu et al., 2013). There were a total of 6 platinum-resistant patients treated across all of the dose levels. The ORR was 50%, with a CBR of 67%. The median PFS was 7.5 months, with a range of 3.3 to 20.4 months. In the 6 patients, there were 3 gBRCAm carriers (confirmed PR [1], unconfirmed PR [1] and SD x 8months [1]) and 3 non-gBRCAm carriers/unknowns (confirmed PRs [2] and 1 SD (<6 months, by CA125 only [1]).

A multi-institutional phase II trial comparing the activity of the cediranib/olaparib capsules combination to olaparib capsules alone in recurrent platinum-sensitive ovarian cancer completed planned accrual of 90 patients in May 2013 and findings from this study were reported in 2014 (NCT01116648, Liu et al. 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.

The combination of cediranib and olaparib capsules significantly extended both PFS and ORR compared to olaparib capsules alone, with a median PFS of 9.0 months for olaparib alone and 17.7 months for cediranib/olaparib (HR 0.42, 95% CI 0.23-0.76, p = 0.005; Fig 3).

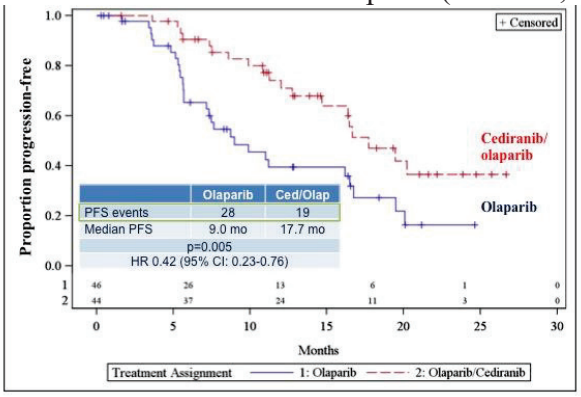


Figure 3. Kaplan-Meier PFS curves in patients treated on olaparib and cediranib/olaparib in Phase 2 trial

There were 2 complete responses (CR) and 20 partial responses (PR) in patients on olaparib capsules alone (48% ORR) and 5 CRs and 30 PRs in patients on cediranib/olaparib capsules (80% ORR, p = 0.002). 47 of the 90 patients enrolled to the phase II cediranib/olaparib vs. olaparib trial were known gBRCAm 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 Fig 4. In gBRCAm carriers, the median PFS was 16.7 months on the olaparib alone arm and 20.2 months on the cediranib/olaparib arm (HR 0.541, 95% CI 0.230-1.26, p = 0.16). In gBRCAm non-carrier/unknown patients, there was a marked increase in PFS from 5.8 months with olaparib alone to 16.6 months with combination therapy in patients with BRCAwt or unknown BRCA status (HR 0.323, 95% CI 0.139-0.746, p = 0.008). The majority of patients on both arms had one or two previous lines of treatment (76% of patients on olaparib alone vs. 82% of patients on cediranib/olaparib arm, however, it is possible that the difference in the ORR and PFS in gBRCAm patients and BRCA non-carrier/unknown patients may be in part due to the degree of prior therapy.

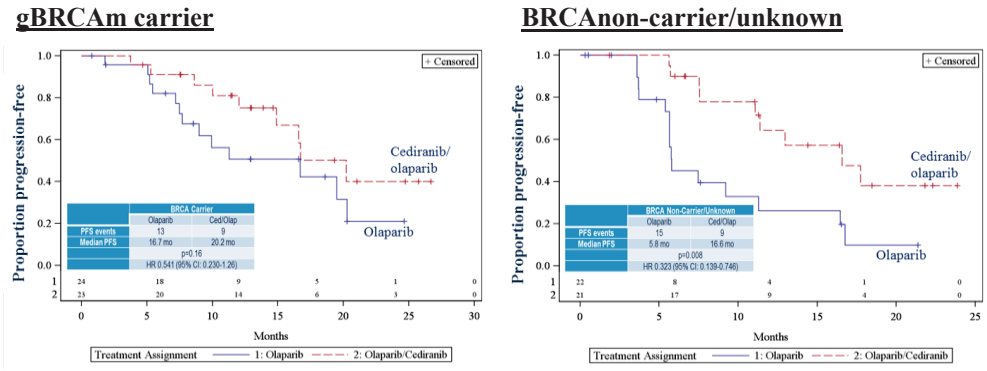


Figure 4. Kaplan-Meier PFS curves in gBRCAm carrier and BRCA non-carrier/unknown patients.

Overall, the combination of cediranib and olaparib demonstrated significantly extended PFS over olaparib alone in women with recurrent, platinum-sensitive ovarian cancer, as measured both by PFS and ORR. The clinical benefit was greater in women with BRCAwt or unknown BRCA status. The platinum-resistant and refractory population is enriched in BRCAwt, non-HRD cancers. Toxicities were consistent with expected class-related toxicities of these drugs.

Differentially occurring grade 3 or 4 toxicities attributed to study treatment included fatigue (27% cediranib/olaparib vs. 11% olaparib), diarrhea (23% vs. 0%), and hypertension (41% vs. 0%). Two grade 4 events 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 had two prior lines of therapy, and had been on combination cediranib/olaparib for ~1 year when she was diagnosed with MDS. 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 MD decision, 5 clinical progressions on cediranib/olaparib vs. 3 withdrawal of consent, 1 MD decision, 6 clinical progressions on olaparib alone).

Tables 1 and 2 summarize the clinical data of cediranib/olaparib combination compared to olaparib or cediranib alone in recurrent ovarian cancers. Olaparib capsules monotherapy response is associated with platinum-sensitivity (Fong et al., 2010); RR of 22% with a clinical benefit rate (CBR, defined as CR, PR and SD≥ 16 weeks) of 52%, and RR of 46% (CBR 69%) were noted in platinum-resistant/refractory, and -sensitive recurrent gBRCAm-associated ovarian cancers, respectively. Gelmon et al. also reported the ORR of 50% (10 of 20) in platinum-sensitive ovarian cancer in the gBRCAm negative cohort, and 60% (3 of 5) in the gBRCAm positive cohort (Gelmon et al., 2011). Lower RRs were noted in platinum-resistant ovarian cancer patients; RR of 33% (4 of 12) in the mutation-positive cohort, and in only 4% (1 of 26) of those in the mutation-negative cohort, respectively (Gelmon et al., 2011). Additionally, Lee and colleagues reported a phase I study of olaparib in capsule formulation and carboplatin in gBRCAm-associated recurrent ovarian cancer; which yielded a RR of 71% (10 of 14) with a median PFS of 16 months (4-45+ months), and 25% (5 of 20) with a median PFS of 13 months (6-40+ months), in platinum-sensitive gBRCAm- and platinum-resistant/refractory gBRCAm-associated recurrent ovarian cancer patients, respectively (Lee et al., 2014). These findings support the olaparib monotherapy may have activity in tumors with DNA repair defects even after acquiring platinum resistance.

Table 1. Comparison of cediranib/olaparib to results of single-agent olaparib in recurrent ovarian cancer trials

Trial	N	PFS	ORR (RECIST) %
Ced/Olap RP2 (platinum-sensitive) (Liu, Lancet Onc 2014)			
Olap capsules 400mg BID	46	9.0	56.1
Ced 30mg QD/olap capsules 200mg BID	44	17.7	83.7
Study 12 (Olap vs. PLD) RP2, PFI<12mo (Kaye, JCO 2012)			
Olap capsules 200mg BID	32	6.5	25
Olap capsules 400mg BID	32	8.8	31
PLD 50mg/m^2	33	7.1	18
Olap capsules single-arm Ph2 (Gelmon, Lancet Onc 2011)			
All ovarian (N = 63; 17 gBRCAm /46 BRCAwt)	63	7.3	29
Platinum-sensitive	25	N/A	52
Platinum-resistant	38	N/A	13

All patients on the phase II study of cediranib had between 0 and 2 lines of prior therapy in the recurrent setting (Matulonis et al., 2009). Majority of women (27 of 30) with platinum-resistant disease, received either 0 or 1 line of prior therapy at recurrence. Overall, eight patients (17%; 95% CI, 7.6% to 30.8%) had a PR, and six patients (13%; 95% CI, 4.8% to 25.7%) had SD. The median PFS was 5.2 months. Grade 3 toxicities (> 20% of patients) included hypertension (46%), fatigue (24%), and diarrhea (13%). Grade 4 toxicities included CNS hemorrhage, hypertriglyceridemia/hypercholesterolemia/elevated lipase, and dehydration/elevated creatinine

(n = 1 for each). A phase I trial was previously conducted to establish the recommended phase II dosing of the cediranib/olaparib capsules combination, which enrolled a total of 28 patients (20 ovarian, 8 breast). RR of 44% to the cediranib/olaparib capsules combination was observed in this phase I population, which included both gBRCAm carrier and non-carrier patients (Liu et al., 2013).

Table 2. Comparison of cediranib/olaparib to results of single-agent cediranib in recurrent ovarian cancer trials

Trial	N	PFS	ORR (RECIST) %
Ced/Olap RP2 (platinum-sensitive) (Liu, Lancet Onc 2014)			
Olap capsules 400mg BID	46	9.0	56.1
Ced 30mg QD/olap capsules 200mg BID	44	17.7	83.7
Ced single-arm Ph2 (Matulonis, JCO 2009)			
Overall	47	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)
Ced single-arm Ph2 (Hirte – abstract ASCO 2008)			
Overall	60	4.1	
Platinum-sensitive	26	(no sig diff	3 PRs (of 17 pts)
Platinum-resistant	34	between groups)	1 PR (of 24 pts)

2.4 Translational Science Background

2.4.1 BROCA-HR and Genomic Scarring

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 recombination (HR)-mediated DNA repair. Other genes in this pathway (*BRIP1/FANCJ, PALB2/FANCN, RAD51C/FANCO, RAD51D*) also contribute to hereditary breast and ovarian cancer (Walsh et al., 2011; Pennington et al., 2012; Meindl et al. 2010; Rafnar et al., 2011; Loveday et al. 2011). 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 (TCGA Network 2011). PARP inhibitors demonstrate synthetic lethality in cells with HRD, including cells deficient in *BRCA1/2* (Bryant et al., 2005; Farmer et al., 2005). Recurrent ovarian carcinomas in *BRCA1/2* mutation carriers have an approximate 40% response rate to PARP inhibitors and also have an increased response to platinum based chemotherapy (Kaye et al.,

2012). Importantly, approximately 25% of serous ovarian cancers that are wildtype for *BRCA1/2* also respond to PARP inhibition (Gelmon et al. 2011).

Germline *BRCA1/2* mutations (gBRCAm) are the prototype molecular alterations that confer HRD (Bryant et al., 2005; Farmer et al., 2005). *BRCA1* and *BRCA2* somatic mutation (sBRCAm) occur in approximately 6% of cases (TCGA Network 2011; Pennington et al., 2013) and also appear to confer sensitivity to PARPi (Lederman et al, 2014). PARP inhibitors also selectively kill cells *in vitro* that are deficient in other homologous recombination (HR) genes including *RAD51D, NBN, ATM,* and *CHEK2* (Loveday et al., 2011; McCabe et al., 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 survival (Pennington et al., 2013). 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 et al., 2013).

In order to respond to a PARP inhibitor, cancer cells need to be deficient in HR but also proficient in the alternative error prone non-homologous end joining (NHEJ) DNA repair pathway (Patel et al., 2011; Adamo et al., 2010). Thus, loss of HR is not, by itself, sufficient for PARP inhibitor sensitivity, and an accurate predictor of PARP inhibitor responsiveness could require assessment of many components of both the HR and NHEJ pathways. A more efficient assay, which would not require a prior knowledge of the critical elements in these DNA repair pathways, would instead measure DNA repair capacity. Recent evidence suggests that *BRCA1/2* deficient cancers exhibit global DNA alterations termed “genomic scarring” that are consistent with their reliance on the NHEJ pathway (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.

Relevance: The marked susceptibility of patients with gBRCAm-associated cancers has validated gBRCAm as a predictive biomarker for PARP inhibitor response (Fong et al., 2009). Other mechanisms of HRD may be a functional biomarker for response to DNA damaging agents and PARP inhibitors. 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. Additional exploratory biomarkers for HRD will include *BRCA1* methylation, *BRCA1* protein expression, and genomic scarring. We hypothesize that the BROCA test will identify subsets of ovarian cancer patients with HRD, and may yield biomarkers with potential to guide administration of this combination for the women we serve.

Preliminary Data*:* BROCA is a targeted capture and massively parallel sequencing assay that is capable of identifying all classes of mutations including gene rearrangements (Wickramanyake et al., 2012; Johnson et al., 2013). 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 et al., 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 (FANCJ), RAD51D, RAD51C (FANCO),* and *PALB2 (FANCN)* (Walsh et al., 2011; Wickramanayake et al., 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 et al., 2014). The presence of either a germline or somatic FA/HR mutation is highly predictive of an improved primary response to platinum chemotherapy ($p<0.0005$, Figure 5) and longer overall survival ($p=0.001$, Figure 6) (Pennington et al., 2014). Germline and somatic loss of function mutations were identified in all of the 13 FA/HR genes evaluated.

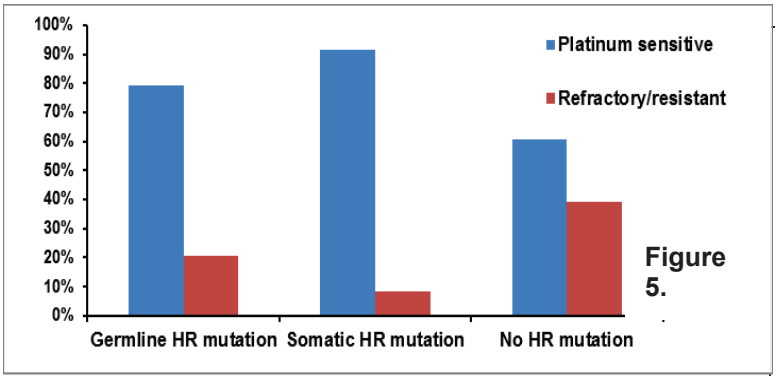


Figure 5.

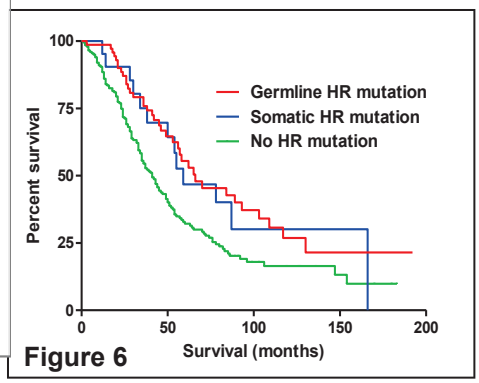


Figure 6

Dr. Swisher's laboratory has designed a new version of BROCA (BROCA-HR) that includes many additional DNA repair genes (65 total genes) as well as 3000 single nucleotide polymorphisms (SNPs). Similar sequencing accuracy and sensitivity sequencing DNA is obtained from formalin fixed paraffin embedded (FFPE), fresh blood, and flash frozen specimens. BROCA-HR includes genes that are targets of both somatic and germline mutations. The BROCA-HR includes genes that regulate HR or NHEJ that, if mutated, could mediate resistance to PARP inhibition such as *TP53BP1* (Bunting et al., 2010; Bouwman et al., 2010). The BROCA design is flexible and can be altered to include any genes of research interest. The current design for BROCA-HR includes the following genes:

BROCA-HR gene list (n=65)
a. BRCA-FA homologous recombination pathway: *ATM, ATR, BABAM1, BAP1, BARD1, BLM, BRCA1, BRCA2 (FANCD1), BRCC3, BRE, BRIP1 (FANCJ), CDK12, CHEK1, CHEK2, ERCC1, ERCC4 (FANCQ), FAM175A (abraxas), FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG (XRCCC9), FANCI, FANCL, FANCM, MRE11A, NBN, PALB2 (FANCO), RAD51C (FANCO), RAD51D, RBBP8 (CtIP), SLX4 (FANCP), UIMC1 (RAP80), XRCC2, XRCC3, XRCC4;*
b. DNA mismatch repair (Lynch syndrome) *MLH1, MSH2 (*and *EPCAM), MSH6, PMS2;*
c. Other DNA repair or surveillance genes: *HELQ, NEIL1, PPM1D, POLD1, POLE, RIF1, TP53;*
d. Other breast cancer genes or related pathways: *GEN1, PTEN, PIK3CA, RINT1;*
e. NHEJ pathway genes*: DCLRE1C, LIG4, PARP1, PRKDC, TOPBP1, XRCC5, XRCC6;*

f. Modifiers of homologous recombination: *CHD4, ID4, PAXIP1, TP53BP1, UPS28.*

A common characteristic of genomic scarring is large (>15Mb) but sub-chromosomal deletions. Therefore, fine mapping of LOH is not necessary to identify the HRD genomic scar. A 3000 SNP assay to define "genomic scarring" has been tested in existing TCGA data (Figure 7). Indeed, using only 3000 SNPs can define cases with high LOH which have better prognosis. Combining the BRCA mutation status and the LOH profile provides additional prognostic information. Therefore, we can assay 3000 SNPs in the same BROCA-HR assay at no additional cost which will provide an LOH profile to assess genomic scarring as an exploratory biomarker.

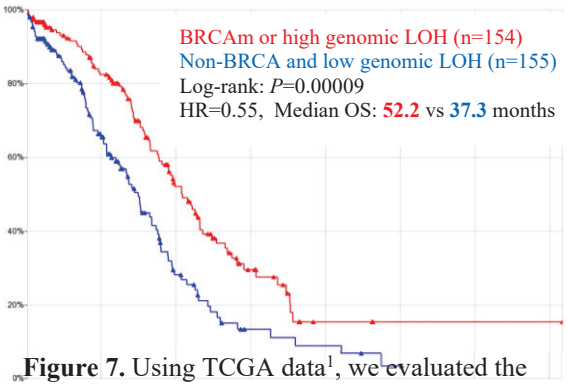


Figure 7. Using TCGA data[1], we evaluated the performance of 3000 SNPs defining high genomic LOH in combination with BRCAm status.

2.4.2 BRCA1 Assays

BRCA1 promoter methylation: BRCA1 promoter methylation down regulates BRCA1 message and protein expression and occurs in 10-15% of ovarian carcinomas (Baldwin et al., 2000; Esteller et al., 2000). Unlike *BRCA1* mutations, *BRCA1* methylation does not correlate with platinum response to therapy or overall survival (Swisher et al., 2009). Therefore, the role of *BRCA1* methylation in PARP inhibitor 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 et al., 2009; Thrall et al., 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.

A variety of techniques for the study of DNA methylation have been developed. Dr. Levine's laboratory utilizes a technique of pyrosequencing, which 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 (R2 > 0.99) for the sequential addition of up to five identical nucleotides (C, G, and T) or three dATPs. In addition, it allows the interrogation of multiple consecutive CpG sites.

The assay utilized by Dr. Levine's laboratory has been validated through the use of 15 samples previously tested through TCGA project. All of the results obtained by pyrosequencing analysis matched with TCGA reported 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, a dilution series experiment using 7 mixtures of methylated DNA (Millipore positive control) and unmethylated genomic DNA (100%, 50%, 25%, 12.5%, 6.25%, 3.125%, and 1.56%) was performed. 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%.

BRCA1 immunohistochemistry (IHC): BRCA1 protein function can be lost through a variety of mechanisms including germline mutation, somatic mutation, and epigenetic silencing. Combined these defects were found in ~30% of high-grade serous ovarian cancers by TCGA. BRCA1 IHC may be a useful candidate to modify response to PARP inhibitor treatment and link to a defect in homologous recombination. Dr. Levine's lab has recently validated a BRCA1 antibody for IHC (Garg et al., 2013). The assay has a high negative predictive value of 92% indicating that it is not likely to show loss of expression in patients without BRCA1 alterations. The positive predictive value is lower at 83% indicating that some alterations may have retained protein expression, however, when the 13% of equivocal cases are excluded this increased to 94% with corresponding high levels of sensitivity and specificity.

2.4.3 Duke 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 (Table 3).

Table 3. Plasma-based marker identification

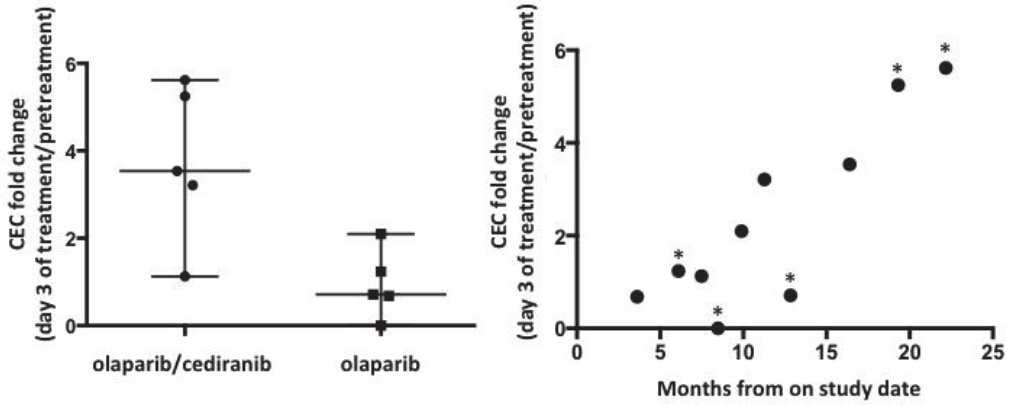
Soluble Angiogenic Factors		Matrix-Derived Factors	Markers of Vascular Activation and Inflammation
ANG-2	PDGF-BB	sEndoglin	CRP
bFGF	PlGF	Osteopontin	ICAM-1
HGF	VEGF-A	TGFb1	IL-6
IGFBP1	VEGF-D	TGFb2	IL-8
IGFBP2	sVEGFR1	TGFbRIII	PAI-1 Active
IGFBP3	sVEGFR2	TIMP1	PAI-1 Total
PDGF-AA	sVEGFR3	TSP2	SDF-1

			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.

2.4.4 Circulating Endothelial Cells (CEC)

Vascular injury is known to be accompanied by an induction in CEC production (Lin et al., 2013). Elevated numbers of CEC have been described in lymphoma, melanoma, and other solid tumors including ovarian cancer, reflecting the perturbation of vascular endothelium (Goon et al., 2006). A related circulating cell population is endothelial progenitor cells (CEP), which originate from the bone marrow rather than from vessel walls and relate to tumor angiogenesis (Rafii et al., 2002). Lee and colleagues recently reported prospectively planned exploratory biomarker endpoints in the phase II study of the combination of olaparib in capsule formulation and cediranib (Lee et al., Front Oncol. 2015). It is hypothesized that 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 CEC (nucleated CD133-CD146+ CD31+CD45-), 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 8A). CEC fold increase pretreatment to day 3 correlated with survival (r=0.88, 95%CI 0.55-0.97, p<0.001; Figure 8B).



A. **B.**

Figure 8. A. Patients receiving olaparib/cediranib had a larger fold 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 alive and progression-free.

CEC/CEP have been examined in early clinical trials using anti-angiogenics (Ning et al., 2010; Park et al., 2013; Kummar et al., 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 et al., 2010); patients with ≥ 75% PSA decline had a increase in CEC levels compared with those who had < 75% PSA decline (p=0.02), indicating an inverse correlation between CEC levels and PSA response to anti-angiogenic therapy.

These exploratory translational studies demonstrate that olaparib/cediranib caused vascular injury indicated by increase of CEC, supporting 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.

2.5 Quality of Life

Although there is a relatively small body of literature examining quality of life (QoL) with recurrent, platinum resistant ovarian cancer, QOL may be maintained for those receiving further chemotherapy, particularly if they are responding to treatment (Beesley et al., Gyn Onc 2014). Similarly, among a sample of recurrent, platinum resistant symptomatic patients, 40% derived a clinical benefit from chemotherapy, and 50% reported symptom improvement (Friedlander et al., IJGC 2014). In the AURELIA trial, patients with platinum-resistant ovarian cancer were randomly assigned to chemotherapy alone, or with bevacizumab. Patients who received bevacizumab with chemotherapy reported a significantly greater improvement in abdominal symptoms and QOL (Stockler et al., JCO 2013), supporting a role for bevacizumab with chemotherapy in the treatment of women with platinum-resistant ovarian cancer. However, in a recent Cochrane report in which QOL data were deemed insufficient for meta-analyses, authors note that much more research is needed to determine the role of PARP inhibitors in platinum-resistant disease (Wiggans et al., Cochrane Database Syst Rev May 2015). Therefore, the effect on QoL of cediranib alone or olaparib alone, or in combination, compared to standard chemotherapy is a critically important and timely question in the setting of platinum resistant disease.

In the absence of an OS benefit, it is difficult 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, these studies require careful assessment of targeted quality of life domains, in particular, disease symptoms, but also treatment side effects, acceptability of therapy and patient functioning.

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 PFS. For this study, the following measures are proposed:

- 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: Two measures of treatment side effects will be employed: 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: Three brief measures of patient function and well-being will be employed: 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).

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. Thus, it is important to evaluate patients' preferences for the attributes of their treatments, including not only OS and PFS, but also the timing and convenience of treatment regimens, symptoms of cancer, side effects of treatments, and health utility out of pocket costs. 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 PRO data from this trial to inform the preference elicitation exercises. As such, it will be necessary 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. (Note 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 IX. A 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 IX. *Within the Phase II trial, these same 27 items will be collected for their use rolling into the Phase III trial.* Excluding these in Phase II would compromise the power to detect between-arm differences in Phase III.

Study Hypotheses and Instrument Selection

It is hypothesized that the treatment arm associated with PFS benefit will also demonstrate a PRO benefit relative to the others. 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 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 (exploratory) emphasis on treatment side effects and burden/acceptability of treatment. The tolerability of biological therapies 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.

A 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 is less than 10 minutes for the entire set of questions majority of patients, 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 et al., 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 et al., 2001), but they have been supplemented, reorganized and validated to create a set of targeted outcome tools for disease related symptoms, treatment side effects, 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 et al., 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.

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.

2.6 Rationale for trial design

It is hypothesized that the combination of cediranib and olaparib will yield greater DNA damage and inhibition in tumor vascularity than single agent alone and/or standard chemotherapies, in women with recurrent platinum-resistant or-refractory ovarian, primary peritoneal, or fallopian tube cancers. These changes are believed to result in clinical benefit, as measured by prolonged PFS and/or OS.

The phase I studies to assess the tolerability of cediranib and olaparib provided insufficient data for assessing the efficacy of these agents. Thus the GY005 design included a 4-arm, randomized phase II study for preliminary efficacy assessment. The component included interim and final analyses to drop treatment arms that failed to reach the defined thresholds for disease specific activity, as measured by PFS (Section 13.1.3).

The RP2 study facilitated selection and testing of the experimental drugs, and allowed patients on the phase II component to contribute to the final phase III endpoint, saving clinical and financial resources. Based on the outcomes of the phase II study, the active monotherapy olaparib arm has been excluded. The RP3 study has been simplified to compare the cediranib+olaparib combination and monotherapy cediranib with physician's choice standard of care chemotherapy (single-agent PLD, weekly paclitaxel, or topotecan) (Section 13.1.3). In addition, the RP3 primary endpoints (PFS and OS), monotherapy cedirinib and the combination of cediranib+olaparib will be compared against standard of care chemotherapy to assess their comparative disease-related symptoms, and tolerability, as assessed by patient report of common side effects. BRCA1/BRCA2-specific biomarkers and angiogenic biomarkers will be evaluated to correlate with treatment outcome and response. The goal of the correlative studies is to identify potential predictive biomarkers that could be utilized to direct targeted therapy.

Patients with recurrent platinum-resistant or-refractory ovarian cancers, without gBRCAm are the enriched patient population with unmet medical needs. There is an urgent need for the development of targeted therapies for this patient population. The results of the phase II/III trials could potentially produce practice-changing results, given that limited data of targeted-therapy in recurrent platinum-resistant or-refractory ovarian cancer patients.

Hence, if positive, the results of this trial may provide a targeted agent alternative for women with recurrent platinum-resistant or-refractory disease with the potential for increased tolerability.

2.7 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. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY 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

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

3.1.1 Patients must have histologically or cytologically confirmed ovarian cancer, peritoneal cancer or fallopian tube cancer and must have a histological diagnosis of either serous or endometrioid cancer based on local histopathological findings. Both endometrioid and serous histology should be high-grade for eligibility of non-mutation carriers.
Patients with clear cell, mixed epithelial, undifferentiated carcinoma, or transitional cell carcinoma 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 BRCA testing through Myriad, Myriad testing will be accepted. If testing for 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 germ line deleterious BRCA 1 or BRCA 2 mutation or BRCA rearrangement is required. **(12/05/2016)**
A copy of Myriad or other BRCA mutational analysis (positive or VUS or negative) reports will be requested but not required for study enrollment.

3.1.2 Patients should have recurrent platinum-resistant or- refractory disease - defined as disease that has progressed by imaging while receiving platinum or had recurrence within 6 months of the last receipt of platinum-based chemotherapy. Rising CA125 only is not considered as platinum-resistant or refractory disease. **(12/05/2016)**

3.1.3 Phase II study: measurable disease by RECIST 1.1 criteria.
If archival tumor sample is not available tumor sample from fresh biopsy is acceptable. **(12/05/2016)**

3.1.4 Phase III study: evaluable disease – defined as RECIST 1.1 measurable disease OR non-measurable 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 in the setting of a CA125 ≥ 2x ULN).

3.1.5 Prior therapy:

3.1.5.1 No more than 3 prior treatment regimens (including primary therapy; no more than 1 prior non-platinum based therapy in the platinum-resistant/-refractory setting). Hormonal therapies used as single agents (i.e. tamoxifen, aromatase inhibitors) will not count towards this line limit. **(12/05/2016)**

3.1.5.2 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.

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

3.1.6 Patient must have provided study specific informed consent prior to study entry.

3.1.7 ECOG performance status 0 or 1 or 2 (see Appendix II).

3.1.8 Patients must have adequate organ and marrow function as defined below **(12/05/2016)**

- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- Hemoglobin ≥ 10 g/dL
- Total bilirubin ≤ 1.5 times the upper limit of normal (ULN) institutional limits
- AST (SGOT)/ALT (SGPT) ≤ 3 × institutional ULN. If intrahepatic liver metastases are present, AST and ALT must be ≤ 5 times institutional ULN.
- Creatinine ≤ 1.5 X the institutional ULN
- Urine protein: creatinine ratio (UPC) of ≤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 2+ proteinuria on dipstick must also have a 24-hour urine collection demonstrating protein of ≤ 500mg over 24 hours.

3.1.9 Toxicities of prior therapy (excepting alopecia) should be resolved to less than or equal to Grade 1 as per CTCAE (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Patients with long-standing stable grade 2 neuropathy may be considered after discussion with the Study Chair.

3.1.10 Adequately controlled blood pressure (SBP ≤140; DBP ≤ 90mmHg) on maximum of three antihypertensive medications. Patients must have a BP of ≤ 140/90 mmHg taken in

the clinic setting by a medical professional within 2 weeks prior to starting study. It is strongly recommended that patients who are on three antihypertensive medications be followed by a cardiologist or a primary care physician for management of BP while on protocol. Patients must be willing and able to check and record daily blood pressure readings. Blood pressure cuffs will be provided to patients randomized to cediranib alone and the combination of olaparib and cediranib arms. Please refer to section 9.6, and Appendix IV. **(12/05/2016)**

3.1.11 Adequately controlled thyroid function, with no symptoms of thyroid dysfunction and TSH within normal limits**. (12/05/2016)**

3.1.12 Able to swallow and retain oral medications and without GI illnesses that would preclude absorption of cediranib or olaparib.

3.1.13 Age ≥ 18 years

3.1.14 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.

3.1.15 Olaparib adversely affects embryofetal survival and development in the rat. 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 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 3 months after the last dose of olaparib. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.2 Ineligibility Criteria

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. **(12/05/2016)**

3.2.2 Any other investigational agents within the past 4 weeks.

3.2.3 Prior treatment affecting the VEGF/VEGFR pathway or the angiopoietin pathway in the recurrent setting, including but not limited to thalidomide, bevacizumab, sunitinib, sorafenib, pazopanib, cediranib, nintedanib, and trebananib. Bevacizumab used in the upfront setting in conjunction with chemotherapy and/or as maintenance to treat newly diagnosed disease will be allowed.

3.2.4 Prior use of PARP-inhibitors.

3.2.5 CA-125 only disease without RECIST 1.1 measurable or otherwise evaluable disease.

3.2.6 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to starting cediranib.

3.2.7 Current signs and/or symptoms of bowel obstruction or signs and/or symptoms of bowel obstruction within 3 months prior to starting study drugs

3.2.8 History of intra-abdominal abscess within the past 3 months.

3.2.9 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. **(12/05/2016)**

3.2.10 Dependency on IV hydration or TPN.

3.2.11 Any concomitant or prior invasive malignancies with the following curatively treated exceptions:

3.2.11.1 Treated limited stage basal cell or squamous cell carcinoma of the skin.

3.2.11.2 Carcinoma in situ of the breast or cervix.

3.2.11.3 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. **(12/05/2016)**

3.2.11.4 Prior cancer treated with a curative intent with no evidence of recurrent disease 5 years following diagnosis and judged by the investigator to be at low risk of recurrence.

3.2.12 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. 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.

3.2.13 Patients with any of the following:

3.2.13.1 History of myocardial infarction within six months

3.2.13.2 Unstable angina

3.2.13.3 Resting ECG with clinically significant abnormal findings.

3.2.13.4 New York Heart Association functional classification of III or IV

.

3.2.14 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:

3.2.14.1 Prior treatment with anthracyclines

3.2.14.2 Prior treatment with trastuzumab

3.2.14.3 Prior central thoracic radiation therapy (RT), including RT to the heart

3.2.14.4 History of myocardial infarction within 6 to 12 months (Patients with history of myocardial infarction within 6 months are excluded from the study)

3.2.14.5 Prior history of impaired cardiac function

3.2.15 History of stroke or transient ischemic attack within six months

3.2.16 Clinical significant peripheral vascular disease or vascular disease (aortic aneurysm or aortic dissection)

3.2.17 Evidence of coagulopathy or bleeding diathesis. Therapeutic anticoagulation for prior thromboembolic events is permitted.

3.2.18 Evidence suggestive of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) on peripheral blood smear or bone marrow biopsy, if clinically indicated.

No prior allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUBCT).

3.2.19 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.

3.2.20 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. **(12/05/2016)**

3.2.21 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.

3.2.22 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 V.

Strong inhibitors and inducers of UGT/PgP should be used with caution. **(12/05/2016)**

3.2.23 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.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

4.1 PHASE II study (12/05/2016)

PRE-TREATMENT ASSESSMENTS

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 (calendar days)	Prior to Cycle 1 Day 1 Treatment (calendar days)
Informed Consent	≤ 28 days	
History and Physical	≤ 28 days	≤ 7 days
Vital Signs (Blood Pressure, Heart Rate, Temperature and Pulse Oxygen Saturation)	≤ 28 days	Day of treatment
Height	≤ 28 days	≤ 7 days
Weight	≤ 28 days	≤ 7 days
Performance Status (ECOG)	≤ 28 days	≤ 7 days
Toxicity Assessment	≤ 14 days	≤ 7 days
Patient Reported Outcome Assessment		≤ 7 days
Concurrent Medications	≤ 14 days	Day of treatment
CBC with Differential	≤ 14 days	≤ 7 days
Chemistries (including Sodium, Potassium, Chloride, bicarbonate, Calcium, Glucose, BUN/Creatinine, Total Bilirubin, Total Protein, ALT (SGPT), AST (SGOT), Alkaline Phosphatase, Albumin)	≤ 14 days	≤ 7 days
Urine protein:creatinine ratio (preferred) or urinalysis	≤ 14 days	≤ 7 days
TSH	≤ 14 days	≤ 7 days [a]
CA125	≤ 14 days	≤ 7 days
Pregnancy Test (for patients of child bearing potential)	≤ 14 days	≤ 3 days[b]
Chest imaging (X-ray or CT scan of the chest)	≤ 28 days	
Radiographic Tumor Measurement (CT or MRI of the abdomen and pelvis)[c]	≤ 28 days	≤ 28 days
Electrocardiogram	≤ 14 days	≤ 7 days
MUGA or echocardiogram[d]	≤ 28 days	

[a] For patients who receive cediranib only.
[b] The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of hCG.
[c] Radiographic tumor measurements should be obtained via imaging of at least the chest, abdomen, and pelvis at baseline. If chest imaging at baseline reveals evidence of measurable disease, then subsequent radiographic tumor assessments must also include chest imaging. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline and subsequent assessments. Contrast CT is the preferred modality.

Tumor reassessment will be time-based at 9 +/- 1 week throughout the study for the first year and every 12 weeks (+/- 7 days) after the first year.
[d] MUGA or echocardiogram should be performed at baseline for all patients at increased risk for compromised LVEF, including patients with 1) prior treatment with anthracyclines, 2) prior treatment with trastuzumab, 3) prior central thoracic RT, or 4) history of myocardial infarction within the 12 months prior. LVEF assessment by MUGA or echocardiogram should be performed on an every 16 week basis for patients with these risk factors on Arm II or Arm III of study treatment.

ASSESSMENTS DURING TREATMENT

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.

Parameter	**Prior to day 1 of each cycle of therapy[1]**	**Every other week for first 8 weeks of study therapy (Arms II, III and IV)**	**After completion or stopping of therapy[2]**
Medical history and physical examination	≤ 1 day of treatment		See footnote [2]
Concomitant medications[3,4]	≤ 1 day of treatment	Day of treatment/assessment	See footnote [2]
Adverse event assessment[4]	≤ 1 day of treatment	Day of treatment/assessment	See footnote [2]
Vital signs (Blood Pressure, Heart Rate, Temperature and Pulse Oxygen Saturation)	Day of treatment/assessment		
ECOG performance status	≤ 1 day of treatment		
CBC with Differential	≤ 3 days of treatment	Day of treatment/assessment	See footnote [2]
Serum chemistry[5]	≤ 3 days of treatment		See footnote [2]
TSH [6]	≤ 3 days of treatment		6 months (+/- 1 week) after stopping study treatment.
Urine protein:creatinine ratio (preferred) or urinalysis	≤ 3 days of treatment		
Electrocardiogram (ECG)[7]	≤ 3 days of treatment		
MUGA or echocardiogram	See footnote [8]		
CA-125 measurement	≤ 3 days of treatment		See footnote [2]
Tumor assessment	See footnote [9]		
Home BP assessment[10]	Twice daily while on study treatment		See footnote [10]

Patient-reported outcome assessment[11]	Every 12 weeks for 2 years, unless the patient withdraws from study participation.		
PK and PD studies	See footnote [12]		

[1] Timing of assessments prior to Cycle 1 Day 1 may be as per pre-treatment assessments schedule. For Cycle 1 Day 1, laboratory evaluations, and ECG do not have to be repeated if they have been performed at screening within 7 days of Cycle 1 Day 1.

[2] 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 (except TSH) should be continued every 9 weeks (+/- 1 week) until time of progression or another therapy is initiated.

[3]: 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.

[4]: Participants on Arms II, III, and IV should be contacted at least once every 2 weeks by phone or assessed in person for the first 8 weeks of therapy to assess for adverse events and concomitant medications. Pre-cycle and off-study AE assessments must be done at a scheduled clinic visit.

[5]: Serum chemistry includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin.

[6]: For patients who receive cediranib. Should be performed pre-study and prior to the first two cycles of treatment for all participants. Additional assessment of thyroid function should be performed as clinically indicated.

[7]: Should be performed pre-study and subsequent ECG should be done only if clinically indicated.

[8]: MUGA or echocardiogram should be performed at baseline for all patients at increased risk for compromised LVEF, including patients with 1) prior treatment with anthracyclines, 2) prior treatment with trastuzumab, 3) prior central thoracic RT, or 4) history of myocardial infarction within the 12 months prior. LVEF assessment by MUGA or echocardiogram should be performed on an every 16 week basis for patients with these risk factors on Arm II or Arm III of study treatment. Additionally, LVEF assessment by MUGA or echocardiogram should be performed every 12 weeks while on treatment for participants receiving Arm I, Regimen II (pegylated liposomal doxorubicin) but not for weekly taxol or topotecan.

[9]: **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 every 9 weeks (+/- 7 days) until progression. An Excel tool is available on the CTSU website to calculate dates of re-imaging. Utilize same imaging modality of abdomen and pelvis +/- chest (for patients with evidence of measurable disease on baseline chest imaging; then subsequent radiographic tumor assessments must also include chest imaging.

[10]: 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 Arms II and 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.

[11]: Patient-reported outcomes should be performed every 12 weeks (+/- 1 week) for 2 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.

[12] PK studies will be done during the phase II study. See section 11.2.1.1 for more details for PK and other correlative study samples collection.

ASSESSMENTS IN FOLLOW UP

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.

Assessments	**From end of treatment:** Follow-up forms (Q forms) are collected for the 5- year follow-up period or until study termination
Vital Status	Every 3 months (+/- 1 week) x 2 years, then every 6 months (+/- 1 week) x 3 years or until death.
Toxicity Assessment	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.
Patient-reported outcome assessments	PRO assessments will continue post-progression every 12 weeks (+/- 1 week) until 2 years from the study enrollment, measured from approximately cycle 1, day 1, unless the patient withdraws from study participation.
Radiography tumor measurement	Every 9 weeks (+/- 7 days) x 1 year, then every 12 weeks (+/- 7 days) until progression if a patient discontinues study treatment for any reason other than progression, confirmed by RECIST 1.1.

4.2 PHASE III study (12/05/2016)

PRE-TREATMENT ASSESSMENTS

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 (calendar days)	Prior to Cycle 1 Day 1 Treatment (calendar days)
Informed Consent	≤ 28 days	
History and Physical	≤ 28 days	≤ 7 days
Vital Signs(Blood Pressure, Heart Rate, Temperature and Pulse Oxygen Saturation)	≤ 28 days	Day of treatment
Height	≤ 28 days	≤ 7 days
Weight	≤ 28 days	≤ 7 days
Performance Status (ECOG)	≤ 28 days	≤ 7 days
Toxicity Assessment	≤ 14 days	≤ 7 days
Patient Reported Outcomes Assessment		≤ 7 days
Concurrent Medications	≤ 14 days	Day of treatment
CBC/Differential/Platelets	≤ 14 days	≤ 7 days
Chemistries (including Sodium, Potassium, Chloride, bicarbonate, Calcium, Glucose, BUN/Creatinine, Total Bilirubin, Total Protein, ALT, AST, Alkaline Phosphatase, Albumin)	≤ 14 days	≤ 7 days
Urine protein:creatinine ratio (preferred) or urinalysis	≤ 14 days	≤ 7 days
TSH	≤ 14 days	≤ 7 days [a]
CA125	≤ 14 days	≤ 7 days
Pregnancy Test (for patients of child bearing potential)	≤ 14 days	≤ 3 days[b]
Chest imaging (X-ray or CT scan of the chest)	≤ 28 days	
Radiographic Tumor Measurement (CT or MRI of the abdomen and pelvis)[c]	≤ 28 days	≤ 28 days
Electrocardiogram	≤ 14 days	≤ 7 days
MUGA or echocardiogram[d]	≤ 28 days	

[a] For patients who receive cediranib only.

[b] The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of hCG.

[c] Radiographic tumor measurements should be obtained via imaging of at least the chest, abdomen, and pelvis at baseline. If chest imaging at baseline reveals evidence of measurable disease, then subsequent radiographic tumor assessments must also include chest imaging. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline and subsequent assessments. Contrast CT is the preferred modality.

Tumor reassessment will be time-based at 9 +/- 1 week throughout the study for the first year and every 12 weeks (+/- 7 days) after the first year.

[d] MUGA or echocardiogram should be performed at baseline for all patients at increased risk for compromised LVEF, including patients with 1) prior treatment with anthracyclines, 2) prior treatment

with trastuzumab, 3) prior central thoracic RT, or 4) history of myocardial infarction within the 12 months prior. LVEF assessment by MUGA or echocardiogram should be performed on an every 16 week basis for patients with these risk factors on Arm II or III of study treatment.

ASSESSMENTS DURING TREATMENT

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.

Parameter	Prior to day 1 of each cycle of therapy[1]	Every other week for first 8 weeks of study therapy (Arms II and III)	After completion or stopping of therapy[2]
Medical history and physical examination	≤ 1 day of treatment		See footnote [2]
Concomitant medications[3,4]	≤ 1 day of treatment	Day of treatment/assessment	See footnote [2]
Adverse event assessment[4]	≤ 1 day of treatment	Day of treatment/assessment	See footnote [2]
Vital signs (Blood Pressure, Heart Rate, Temperature and Pulse Oxygen Saturation)	Day of treatment/assessment		
ECOG performance status	≤ 1 day of treatment		
CBC with Differential[13]	≤ 3 days of treatment	Day of treatment/assessment	See footnote [2]
Serum chemistry[5]	≤ 3 days of treatment		See footnote [2]
TSH [6]	≤ 3 days of treatment		6 months (+/- 1 week) after stopping study treatment.
Urine protein:creatinine ratio (preferred) or urinalysis[14]	≤ 3 days of treatment		
Electrocardiogram (ECG)[7]	≤ 3 days of treatment		
MUGA or echocardiogram	See footnote [8]		
CA-125 measurement	≤ 3 days of treatment		See footnote [2]
Tumor assessment	See footnote [9]		

Home BP assessment[10]	Twice daily while on study treatment		See footnote [10]
Patient-reported outcome assessment[11]	Every 12 weeks for 2 years, unless the patient withdraws from study participation.		
PD studies	See footnote [12]		

[1] Timing of assessments prior to Cycle 1 Day 1 may be as per pre-treatment assessments schedule. For Cycle 1 Day 1, laboratory evaluations, and ECG do not have to be repeated if they have been performed at screening within 7 days of Cycle 1 Day 1.

[2] 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 (except TSH) should be continued every 9 weeks (+/- 1 week) until time of progression or another therapy is initiated.

[3]: 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.

[4]: Participants on Arms II and III should be contacted at least once every 2 weeks by phone or assessed in person for the first 8 weeks of therapy to assess for adverse events and concomitant medications. Pre-cycle and off-study AE assessments must be done at a scheduled clinic visit.

[5]: Serum chemistry includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin.

[6]: Should be performed pre-study and prior to the first two cycles of treatment for all participants. Additional assessment of thyroid function should be performed as clinically indicated.

[7]: Should be performed pre-study and subsequent ECG should be done only if clinically indicated.

[8]: MUGA or echocardiogram should be performed at baseline for all patients at increased risk for compromised LVEF, including patients with 1) prior treatment with anthracyclines, 2) prior treatment with trastuzumab, 3) prior central thoracic RT, or 4) history of myocardial infarction within the 12 months prior. LVEF assessment by MUGA or echocardiogram should be performed on an every 16 week basis for patients with these risk factors on Arm II or Arm III of study treatment. Additionally, LVEF assessment by MUGA or echocardiogram should be performed every 12 weeks while on treatment for participants receiving Arm I, Regimen II (pegylated liposomal doxorubicin) but not for weekly taxol or topotecan.

[9]: **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 every 9 weeks (+/- 7 days) until progression. An Excel tool is available on the CTSU website to calculate dates of re-imaging. Utilize same imaging modality of abdomen and pelvis +/- chest (for patients with evidence of measurable disease on baseline chest imaging; then subsequent radiographic tumor assessments must also include chest imaging.

[10]: 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 Arms II and 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.

[11]: Patient-reported outcomes should be performed every 12 weeks (+/- 1 week) for 2 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.

[12] See section 11.2.1.1 for more details for PK and other correlative study samples collection.

[13] For patients receiving weekly paclitaxel or topotecan, CBC with differential will be obtained ≤ 1 day prior to days 8, 15, 22 for paclitaxel, and days 8 and 15 for topotecan.

[14] For patients on the cediranib containing arms (arms 2 and 3) only

ASSESSMENTS IN FOLLOW UP

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.

Assessments	**From end of treatment:** Follow-up forms (Q forms) are collected for the 5 year follow-up period or until study termination.
Vital Status	Every 3 months (+/- 1 week) x 2 years, then every 6 months (+/- 1 week) x 3 years or until death.
Toxicity Assessment	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.
Patient-reported outcome assessments	PRO assessments will continue post-progression every 12 weeks (+/- 7 days) until 2 years from the study enrollment, measured from approximately cycle 1, day 1, unless the patient withdraws from study participation.
Radiography tumor measurement	Every 9 weeks (+/- 7 days) x 1 year, then every 12 weeks (+/- 7 days) until progression if a patient discontinues study treatment for any reason other than progression, confirmed by RECIST 1.1.
Subsequent therapy assessment	Patients will be followed every 3 months (+/- 1 week) x 2 years, then every 6 months (+/- 1 week) x 3 years after progression on study treatment, to capture data including 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.

5. TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEURE

5.1 Treatment plan

For the Phase II study, 4 treatments regimens were randomly assigned 1:1:1:1 to incoming patients. In July 2018, the Data Monitoring Committee voted to exclude the olaparib alone regimen. In the Phase III study, the 3 selected treatments will be randomly assigned 1:1:1 to incoming patients. Phase II patients assigned to the selected treatment regimens will be included in the Phase III accrual, and will support the Phase III analyses.

The Phase II and Phase III studies are open-label, and the treatments are administered in an outpatient setting. Patients continue treatment until death, disease progression, unacceptable toxicity, or consent withdrawal. Patients may continue to be followed for up to five years after completion of their protocol therapy.

Duration of Therapy
In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

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. An Excel tool will be provided to sites to assist in determining imaging dates.

Treatment window (12/05/2016)
For 21 or 28 day cycles of Arm 1, 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 treated with the experimental therapies (cediranib and/or olaparib, Arms 2-4), 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 the experimental drug arms (cediranib and/or olaparib, Arms 2-4) 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 1, it will be acceptable for individual chemotherapy doses to be delivered within 24 hours before and after the protocol-defined date for Day 1 of weekly treatment or 21- or 28- day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, the treatment window includes the preceding Thursday (1 day earlier than due) through the following Monday (day 3 past due).

For patients on the experimental drug therapies (cediranib and/or olaparib, Arms 2-4), it will be acceptable for the Day 1 visit of each cycle to take place within 72 hours before or after the protocol-defined date.

No modification of the regimens is allowed.

5.1.1 Phase II study Arms/regimens

5.1.1.1 Arm 1 (Reference Regimen): Physician's choice standard of care chemotherapy:

Patients randomized to the non-platinum-based chemotherapy arm may be treated with one of the three regimens specified in this section per investigator discretion (the planned regimen must be specified prior to randomization). The number of cycles of therapy should be administered as clinically appropriate. After completion of chemotherapy, patients will be followed without further chemotherapy or maintenance therapy until disease progression.

- Regimen 1: Paclitaxel 80 mg/m^2 intravenously (IV) over approximately 60 minutes on days 1, 8, 15, and 22 every 28 days

- Regimen 2: Pegylated liposomal doxorubicin 40 mg/m^2 IV over approximately 60 minutes on day 1, every 28 days

- Regimen 3: Topotecan 4 mg/m^2 IV over approximately 30 minutes on days 1, 8, and 15 every 28 days or 1.25 mg/m^2 IV over approximately 30 minutes on days 1 to 5 every 21 days.

- **No modification** of the assigned regimens, such as additional drugs (gemcitabine, or bevacizumab) is allowed. **(12/05/2016)**

5.1.1.2 Arm 2: Cediranib and olaparib. **(12/05/2016)**

Cediranib 30 mg orally once daily and olaparib 200 mg in tablet formulation orally twice daily continuous dosing. The starting doses of 30mg can be taken as two 15mg tablets. Cediranib should be taken on an empty stomach in the morning approximately one hour before taking the morning dose of olaparib. Olaparib should be taken twice a day approximately 12 hours apart.

One cycle will be considered 28 days. Cycles are continuously numbered regardless of any dose holds or interruptions.

Patients will need to keep medication and blood pressure diaries while taking either oral medication or both and for a cediranib-containing regimen, respectively. A blood pressure cuff will be provided to patients randomized to Arms 2 and 3.

5.1.1.3 Arm 3: Cediranib **(12/05/2016)**

Cediranib 30 mg orally daily continuous dosing. Cediranib should be taken on an empty stomach in the morning. The starting doses of 30mg can be taken as two 15mg tablets.

One cycle will be considered 28 days. Cycle days are continuously numbered regardless of any dose holds or interruptions.

Patients will need to keep medication and blood pressure diaries while taking cediranib.

5.1.1.4 Arm 4: Olaparib **(12/05/2016)**

Olaparib 300 mg 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.

5.1.2 Phase III study Arms/regimens

Patients will be randomized to one of 3 treatment regimens: the standard chemotherapy arm, the combination of cediranib and olaparib arm and the cediranib alone arm.

Duration of Therapy
In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.1.2.1 Arm 1 (Reference Regimen): Physician’s choice standard of care chemotherapy:

Patients randomized to the non-platinum-based chemotherapy arm may be treated with one of the three regimens specified in this section per investigator discretion (the planned regimen will be specified prior to randomization). The number of cycles of therapy should be administered as

clinically appropriate. After completion of chemotherapy, patients will be followed without further chemotherapy or maintenance therapy until disease progression.

- Regimen 1: Paclitaxel 80 mg/m^2 intravenously (IV) over approximately 60 minutes on days 1, 8, 15, and 22 every 28 days

- Regimen 2: Pegylated liposomal doxorubicin 40 mg/m^2 IV over approximately 60 minutes on day 1, every 28 days

- Regimen 3: Topotecan 4 mg/m^2 IV over approximately 30 minutes on days 1, 8, and 15 every 28 days or 1.25 mg/m^2 IV over approximately 30 minutes on days 1 to 5 every 21 days.

- **No modification** of the assigned regimens, such as additional drugs (gemcitabine or bevacizumab) is allowed. **(12/05/2016)**

5.1.2.2 Arm 2: Cediranib and olaparib. **(12/05/2016)**

Cediranib 30 mg orally once daily and olaparib 200 mg in tablet formulation orally twice daily continuous dosing. The starting doses of 30mg can be taken as two 15mg tablets. Cediranib should be taken on an empty stomach in the morning approximately one hour before taking the morning dose of olaparib. Olaparib should be taken twice a day approximately 12 hours apart.

One cycle will be considered 28 days. Cycles are continuously numbered regardless of any dose holds or interruptions.

Patients will need to keep medication and blood pressure diaries while taking either oral medication or both and for a cediranib-containing regimen, respectively. A blood pressure cuff will be provided to patients randomized to Arm 2.

5.1.2.3 Arm 3: Cediranib **(12/05/2016)**

Cediranib 30 mg orally daily continuous dosing. Cediranib should be taken on an empty stomach in the morning. The starting doses of 30mg can be taken as two 15mg tablets.

Patients will need to keep medication and blood pressure diaries while taking cediranib.

One cycle will be considered 28 days. Cycles are continuously numbered regardless of any dose holds or interruptions.

6. TREATMENT MODIFICATIONS/MANAGEMENT

Dose delays and modifications will be made using the following recommendations.

Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE). CTCAE is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).
For adverse events (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 Study Chair.

All AEs experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

There will be no dose escalations or re-escalations on this study.

6.1 Reference regimens (Arm I)

Table 6.1.A: Guidelines for permanent dose reductions, Reference Regimens

Drug	Initial dose level	First reduction	Second reduction
Paclitaxel[1]	80 mg/m^2	Decrease dose to 70 mg/m^2	Decrease dose to 60 mg/ m^2
Pegylated liposomal doxorubicin	40 mg/m^2	Decrease dose to 30 mg/m^2	Decrease dose to 20 mg/ m^2
Topotecan weekly	4 mg/m^2	Decrease dose to 3.5 mg/m^2	Decrease dose to 3 mg/m^2
Topotecan mg/m^2 per day over 5 days	1.25 mg/m^2	Decrease dose to 1 mg/m^2	Decrease dose to 0.75 mg/m^2

[1]Up to 2 dose reductions (70 mg/m^2 and 60 mg/m^2) are acceptable for paclitaxel. Instead of a second dose reduction, 70 mg/m^2 can be maintained if subsequently a one weekly dose is omitted within one cycle. For selected patients, after discussion with Study Chair, a third dose reduction in paclitaxel to 60 mg/m^2 days #1, #8, and #15 can be considered.

6.1.1 Hematologic Issues

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 (EPO) 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.
- Transfusions may be administered as clinically indicated for management of anemia.
- Patients will NOT receive prophylactic thrombopoietic agents.
- Patients may NOT receive amifostine.
- Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below for each regimen.
- **All Arms require ANC of 1500/mm^3 and platelets of 100,000/mm^3 for treatment initiation, the start of each cycle (Day #1), and treatment resumption after holding treatment.**

6.1.1.2 Arm I, Regimen I: Weekly paclitaxel

Dose reductions for next course will be performed according to following guidelines for nadir:

Table 6.1.1.2.A: Dose modifications for neutropenia, Paclitaxel

	Hematologic Event	Dose Modification
Initial Occurrence	Febrile Neutropenia[†] Grade 4 neutropenia (< 500/mm^3) lasting ≥7 days ANC < 1000/mm3 on Day 1 Treatment delays > 7 days for neutropenia	Reduce paclitaxel dose to 70 mg/m^2
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce paclitaxel dose to 60 mg/m^{2}[††]
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue paclitaxel

[†] Febrile neutropenia is defined within the CTCAE as a disorder characterized by an ANC <1000/mm3 and a single temperature of >101 degrees F or a sustained degree of ≥ 100.4 degrees F for more than an hour.
[††]Up to 2 dose reductions (70 mg/m^2 and 60 mg/m^2) are acceptable for paclitaxel. Instead of a second dose reduction, 70 mg/m^2 can be maintained if subsequently a one weekly dose is omitted within one cycle. For selected patients, after discussion with Study Chair, a third dose reduction in paclitaxel to 60 mg/m^2 days #1, #8, and #15 can be considered.

Table 6.1.1.2.B: Dose modifications for thrombocytopenia, Paclitaxel

	Hematologic Event	Dose Modification
Initial Occurrence	Any occurrence of grade 4 thrombocytopenia (platelets < 25,000/ mm^3) Grade 3 thrombocytopenia with bleeding event (platelets 25,000 to <50,000/ mm^3) Severe Bleeding	Reduce paclitaxel dose to 70 mg/m^2
Any Occurrence	Severe Bleeding associated with Febrile Neutropenia	Discontinue paclitaxel
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce paclitaxel dose to 60 $mg/m^{2\dagger}$
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue paclitaxel
†Up to 2 dose reductions (70 mg/m^2 and 60 mg/m^2) are acceptable for paclitaxel. Instead of a second dose reduction, 70 mg/m^2 can be maintained if subsequently a one weekly dose is omitted within one cycle. For selected patients, after discussion with Study Chair, a third dose reduction in paclitaxel to 60 mg/m^2 days #1, #8, and #15 can be considered.		

6.1.1.2.1 Hematologic toxicity

The WBC count must be ≥ 3000/mm3, ANC ≥ 1500/mm3 and the platelet count ≥ 100,000/mm3 prior to the beginning of the following course of treatment on day 1.

The day 8, 15, and 22 paclitaxel dose will not be given unless the ANC is at least 500/mm3 and the platelet count is as least 50,000/mm3. If not given, these doses are omitted and not made up.

For patients who do not achieve hematological recovery on scheduled day of the course, complete blood counts should be performed twice weekly until the above defined limits are achieved. If hematological recovery is achieved within 14 days after the scheduled day of the course, the full dose of paclitaxel adjusted for the previous nadir should be administered immediately. If hematological recovery is not achieved 14 days or more after the scheduled day of the course, the patient will discontinue treatment.

No more than two dose-reductions because of postponed treatment are permitted. However, instead of a second paclitaxel dose reduction, 70 mg/m^2 can be maintained if subsequently a one weekly dose is omitted within one cycle. For selected patients, after discussion with Study Chair, a third dose reduction in paclitaxel to 60 mg/m^2 days #1, #8, and #15 can be considered.

6.1.1.2.2 Non-hematologic toxicity

- Management of non-hematologic toxicities on the reference arm should be per institutional practice and guidelines *except* for mucositis, cutaneous, and hepatic toxicity as noted below. 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.A.

- Other Major Organ Toxicity (not evaluated as disease related): If the patient has any clinically significant non-hematological drug related toxicity CTCAE grade > 3, the patient should discontinue protocol therapy unless strong clinical benefit and discussion with the Study Chair.
- Dose modifications for alopecia, nausea, constipation, or electrolyte abnormalities 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.

6.1.1.2.2.1 Mucositis and cutaneous toxicity

The occurrence of mucositis and cutaneous toxicity grade > 2 leads to a dose reduction of one level. A second occurrence will lead to a second dose reduction of one level. A third occurrence will lead to discontinuation of patient from protocol-directed therapy

6.1.1.2.2.2 Hypersensitivity premedication and infusion related reactions **(12/05/2016)**

Premedication prior to paclitaxel should be administered in accordance with local standard of care in order to prevent severe hypersensitivity reactions associated with paclitaxel. An example of premedication is as follows:

- Dexamethasone 20 mg IV 30 minutes prior to paclitaxel
- An anti-histamine H1 (diphenhydramine 25-50 mg IV or orally, or an equivalent dose of an alternate H1blocker such as loratadine or fexofenadine) 30 minutes prior to paclitaxel
- A standard dose of antihistamine H2 IV (such as cimetidine, ranitidine, or famotidine) 30 minutes prior to paclitaxel
- 5HT3 Antagonist Single dose IV 30 minutes prior to paclitaxel

Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available. Signs or symptoms of a hypersensitivity reaction may include chest tightness, back pain, diffuse erythroderma, dyspnea, tachycardia, hypertension, hypotension, and sensation of extreme anxiety. Significant hypersensitivity reactions as characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in <1% of patients receiving paclitaxel after adequate premedication. These reactions are probably histamine-mediated.

Of note, the occurrence of a hypersensitivity reaction is not considered a dose-limiting toxicity. Patients experiencing a hypersensitivity reaction may be retreated at full doses under institutional protocols to prevent hypersensitivity reactions. See additional treatment and management options below. Sites may also follow institutional guidelines for prevention and/or avoidance of hypersensitivity reactions.

Table 6.1.1.2.2.2A. Hypersensitivity Reactions		
Infusion Reaction	Definition	Appropriate Treatment and Management
Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Stop infusion immediately. May consider retreatment. Treat per institutional guidelines. Patients can also discontinue therapy at the discretion of the investigator.
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. Treat per institutional guidelines. Patients can also discontinue therapy at the discretion of the investigator. Consider diphenhydramine 50 mg IVP and hydrocortisone 100 mg IV piggy back. Consider reinitiation of paclitaxel infusion approximately 30 minutes after initially stopping its administration as long as there is complete resolution of signs and symptoms of the reaction (Markman et al., 2000). See information regarding desensitization below.
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 sequelae.	Stop infusion immediately. May consider desensitization. Treat per institutional guidelines. Patients can also discontinue therapy at the discretion of the investigator. For desensitization: Consider dexamethasone 20 mg po the night before and the morning of treatment. Consider adding anti-histamines such as diphenhydramine 25-50 mg IV, and H2 blockers such as famotidine 20 mg IV, or ranitidine (50 mg IV, and lorazepam 0.5-1 mg po or IV as needed for anxiety can be added as premedications. Consider paclitaxel 2 mg in NS IV starting 30 minutes after treatment with premedications. If reaction, then STOP; give diphenhydramine 50 mg IV push and hydrocortisone 100 mg IV piggy back. Start again 30 minutes after symptoms subside. Then paclitaxel 10 mg in NS IV starting 60 minutes after treatment time. Then paclitaxel 175 mg/m^2 IV starting 90 minutes after treatment time (Markman et al., 2000). Check with institutional pharmacy guidelines regarding dosing, dilution in NS, and administration.

		A patient who develops dyspnea and hypotension with premedication should not be rechallenged.
Grade 4	Life-threatening consequences; urgent intervention indicated.	Do not rechallenge. Paclitaxel should be discontinued.

6.1.1.2.2.3 Modifications for hepatic toxicity

Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1. If no recovery after 2 weeks, patient should discontinue drug.

A second occurrence will lead to a second dose reduction of one level. A third occurrence will lead to discontinuation of patient from protocol-directed therapy.

6.1.1.3 Arm I, Regimen II: Pegylated liposomal doxorubicin (PLD)

Dose reductions for next course will be performed according to following guidelines for nadir:

Table 6.1.1.3.A: Dose modifications for neutropenia, PLD

	Hematologic Event	Dose Modification
Occurrence	500–< 1,500/ mm^3	Wait until ANC ≥ 1,500/ mm^3; redose with no dose reduction
Initial Occurrence	Grade 4 neutropenia (< 500/mm^3)	Wait until ANC ≥ 1,500/ mm^3; reduce PLD dose to 30 mg/m^2
Second Occurrence	Grade 4 neutropenia (< 500/mm^3)	Wait until ANC ≥ 1,500/ mm^3; reduce PLD dose to 20 mg/m^2
Third occurrence	Grade 4 neutropenia (< 500/mm^3)	Discontinue PLD

Table 6.1.1.3.B: Dose modifications for thrombocytopenia, PLD

	Hematologic Event	Dose Modification
Occurrence	25,000–< 75,000/ mm^3	Wait until platelets ≥ 100,000/ mm^3; redose with no dose reduction
Initial Occurrence	Any occurrence of grade 4 thrombocytopenia (platelets < 25,000/mcL) or Severe bleeding	Wait until platelets ≥ 100,000/ mm^3; reduce PLD dose to 30 mg/m^2
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Wait until platelets ≥ 100,000/ mm^3; reduce PLD dose to 20 mg/m^2
Third occurrence	If any of the above toxicities occur after initial dose reduction	Discontinue PLD

6.1.1.3.1 Hematologic toxicity

The WBC count must be ≥ 3000/mm^3, ANC ≥ 1500/mm^3 and the platelet count ≥ 100,000/mm^3 prior to the beginning of the following course of treatment on day 1.

For patients who do not achieve hematological recovery on scheduled day of the course, complete blood counts should be performed twice weekly until the above defined limits are achieved. If hematological recovery is achieved within 14 days after the scheduled day of the course, the full dose of PLD adjusted for the previous nadir should be administered immediately. If hematological recovery is not achieved 14 days or more after the scheduled day of the course, the patient will discontinue treatment.

No more than two dose-reductions because of postponed treatment are permitted.

6.1.1.3.2 Non-hematologic toxicity

- Management of non-hematologic toxicities on the reference arm should be per institutional practice and guidelines except for mucositis, cutaneous, stomatitis and hepatic toxicity as noted below. 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.A.

  Other Major Organ Toxicity (not evaluated as disease related): If the patient has any clinically significant non-hematological drug related toxicity CTCAE grade > 3, the patient should discontinue protocol therapy unless strong clinical benefit and discussion with the Study Chair.

- Dose modifications for alopecia, nausea, constipation, or electrolyte abnormalities 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.

6.1.1.3.2.1 Mucositis and cutaneous toxicity

In case of grade ≥2 hand-foot syndrome (HFS) or stomatitis, the pegylated liposomal doxorubicin (PLD) dose will be delayed until resolved to grade ≤1 or discontinued if not resolved within 2 weeks. In addition, subsequent doses will be reduced if the HFS or stomatitis is grade ≥3. The following tables show the dose modifications for PLD and the course delays recommended as a function of the occurrence and severity of mucositis and cutaneous toxicity, respectively.

Table 6.1.1.3.2.1A: PLD Dose Modification Guidelines for Hand-Foot Syndrome (HFS)	
Toxicity Grade	**Dose Adjustment**
1: mild erythema, swelling, or desquamation not interfering with daily activities	**Redose unless patient has experienced previous Grade 3 or 4 HFS.** If so, delay up to 2 weeks and decrease reduce 1 dose level. Return to original dose interval.
2: erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations <2 cm in diameter	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, PLD should be discontinued. If resolved to Grade 0-1 within 2 weeks and there are no prior Grade 3-4 HFS, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3–4 toxicity, continue treatment with reduce 1 dose level.and return to original dose interval.
3: blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	**Delay dosing up to 2 weeks or until resolved to Grade 0–1.** Reduce 1 dose level.and return to original dose interval. If after 2 weeks there is no resolution, PLD should be discontinued.
4: diffuse or local process causing infectious complications, or a bed ridden state or hospitalization	**Delay dosing up to 2 weeks or until resolved to Grade 0–1.** Reduce 1 dose level and return to original dose interval. If after 2 weeks there is no resolution, PLD should be discontinued.

Table 6.1.1.3.2.1B: PLD Dose Modification Guidelines for Stomatitis	
Toxicity Grade	**Dose Adjustment**
1: painless ulcers, erythema, or mild soreness	**Redose unless patient has experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and reduce 1 dose level. Return to original dose interval.
2: painful erythema, edema, or ulcers, but can eat	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, PLD should be discontinued. If resolved to Grade 0-1 within 2 weeks and there are no prior Grade 3-4 stomatitis, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3–4 toxicity, continue treatment with a 1 dose level reduction and return to original dose interval.
3: painful erythema, edema, or ulcers, and cannot eat	**Delay dosing up to 2 weeks or until resolved to Grade 0–1.** Reduce 1 dose level and return to original dose interval. If after 2 weeks there is no resolution, PLD should be discontinued.
4: requires parenteral or enteral support	**Delay dosing up to 2 weeks or until resolved to Grade 0–1.** Reduce 1 dose level and return to original dose interval. If after 2 weeks there is no resolution, PLD should be discontinued.

6.1.1.3.2.2 Modifications for hepatic toxicity

Limited clinical experience exists in treating patients with hepatic impairment with PLD. The pharmacokinetics of PLD has not been adequately evaluated in patients with hepatic impairment. Doxorubicin is eliminated in large part by the liver. Reduce PLD for serum bilirubin of 1.2 mg/dL or higher.

Based on experience with doxorubicin HCl, it is recommended that the PLD dosage be reduced if the bilirubin is elevated as follows:

serum bilirubin 1.2 to 3 mg/dL: give 20mg/m^2
serum bilirubin > 3 mg/dL: discontinue treatment

6.1.1.3.2.3 Hypersensitivity: Infusion related reactions

Serious and sometimes life-threatening infusion-related reactions can occur with PLD including flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension. The majority of infusion-related events occurred during the first infusion. Seven percent of women with ovarian cancer treated on clinical trials with PLD experienced acute infusion-related reactions and all reactions occurred during cycle 1.

Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available. Signs or symptoms of a hypersensitivity reaction may include chest tightness, back pain, diffuse erythroderma, dyspnea, tachycardia, hypertension, hypotension, and sensation of extreme anxiety. In case of a hypersensitivity reaction, the infusion will be stopped immediately and patient treated per institutional guidelines. If the reaction is completely disappeared, the infusion might be continued at a reduced infusion velocity. See additional treatment and management options below.

Table 6.1.1.3.2.3A. Hypersensitivity Reactions

Infusion Reaction	Definition	Appropriate Treatment and Management
Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Stop infusion immediately. May consider retreatment. Treat per institutional guidelines. Patients can also discontinue therapy at the discretion of the investigator.
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. Treat per institutional guidelines. Patients can also discontinue therapy at the discretion of the investigator. Consider retreatment if resolution of symptoms. Resume PLD infusion at a reduced rate of 1 mg/min and increase rate as tolerated [see PLD package insert]. Discontinue PLD infusion for

		serious or life-threatening infusion-related reactions. Anti-histamines such as diphenhydramine 25-50 mg IV, and H2 blockers such as famotidine 20 mg IV, or ranitidine (50 mg IV, and lorazepam 0.5-1 mg po or IV as needed for anxiety can be added as premedications.
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 sequelae.	Stop infusion immediately. May consider desensitization. Treat per institutional guidelines. Patients can also discontinue therapy at the discretion of the investigator. For desensitization: Consider dexamethasone 20 mg po the night before and the morning of treatment. Consider adding anti-histamines such as diphenhydramine 25-50 mg IV, and H2 blockers such as famotidine 20 mg IV, or ranitidine (50 mg IV, and lorazepam 0.5-1 mg po or IV as needed for anxiety as premedications. PLD infusion at a reduced rate of 1 mg/min and increase rate as tolerated [see PLD package insert] or may follow formal desensitization protocol (Castells et al., 2008). Discontinue PLD infusion for serious or life-threatening infusion-related reactions. A patient who develops dyspnea and hypotension with premedication should not be rechallenged.
Grade 4	Life-threatening consequences; urgent intervention indicated.	Do not rechallenge. PLD should be discontinued.

6.1.1.4 Arm I, Regimen III: Topotecan

6.1.1.4.1 Weekly topotecan administration: definition of dose levels

In the weekly schedule, the minimal infusion dose of topotecan is 3 mg/m^2. Standard dose-adjustments based on observed toxicities should be made, as follows:

The WBC count must be ≥ 3000/mm^3, ANC ≥ 1500/mm^3 and the platelet count ≥ 100,000/mm^3 prior to the beginning of the following course of treatment on day 1.

The day 8, and 15 topotecan dose will not be given unless the ANC is at least 1000/mm^3 and the platelet count is as least 75,000/mm^3. If day 8 dosing criteria are not met, hold the dose and treat on day 15 as planned if toxicity has resolved. If day 15 dosing criteria are not met, hold the dose. Start the next full cycle (i.e. Day 1 treatment) one week later if toxicity has resolved. If day 8 and

15 dosing criteria are not met, yet the patient's counts recover within 2 weeks**,** start the next full cycle at 1 dose reduction level lower.

For patients who do not achieve hematological recovery on scheduled day of the course, complete blood counts should be performed twice weekly until the above defined limits are achieved. If hematological recovery is achieved within 14 days after the scheduled day of the course, the full dose of topotecan adjusted for the previous nadir should be administered immediately. If hematological recovery is not achieved 14 days or more after the scheduled day of the course, the patient will discontinue treatment.

Table 6.1.1.4.1.A: Dose modifications for neutropenia, Weekly Topotecan		
	Hematologic Event	Dose Modification
Initial Occurrence	Febrile Neutropenia[†] Grade 4 neutropenia (< 500/mm3 lasting ≥7 days	Reduce weekly topotecan dose to 3.5 mg/m^2
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce weekly topotecan dose to 3 mg/m^2
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue topotecan
[†] Febrile neutropenia is defined within the CTCAE as a disorder characterized by an ANC <1000/ mm^3 and a single temperature of >101 degrees F or a sustained degree of ≥ 100.4 degrees F for more than an hour. *If day 8 and 15 dosing criteria are not met, yet the patient's counts recover within 2 weeks**,** start the next full cycle at 1 dose reduction level lower.		

Table 6.1.1.4.1.B: Dose modifications for thrombocytopenia, Weekly Topotecan		
	Hematologic Event	Dose Modification
Initial Occurrence	Any occurrence of grade 4 thrombocytopenia (platelets < 25,000/ mm^3) or Severe bleeding	Reduce weekly topotecan dose to 3.5 mg/m^2
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce weekly topotecan dose to 3 mg/m^2
Third occurrence	If any of the above toxicities occur after initial dose reduction	Discontinue topotecan
*If day 8 and 15 dosing criteria are not met, yet the patient's counts recover within 2 weeks**,** start the next full cycle at 1 dose reduction level lower.		

6.1.1.4.2 Topotecan administration in the 5-day schedule: definition of dose levels

In the daily schedule, the minimal infusion dose of topotecan is 0.75 mg/m^2. Subsequent cycles

of therapy (i.e. Day 1 treatment) will not begin until the ANC is ≥ 1500/mm^3 and the platelet count is ≥ 100,000/mm^3. Standard dose-adjustments based on observed toxicities should be made, as follows:

Table 6.1.1.4.2.A: Dose modifications for neutropenia, 5-day Topotecan		
	Hematologic Event	Dose Modification
Initial Occurrence	Febrile Neutropenia[†] Grade 4 neutropenia (< 500/mm^3) lasting ≥7 days Grade 3 neutropenia (500-900/ mm^3) lasting beyond Day 21 of the treatmer course or associated with fever or infection	Reduce topotecan dose to 1 mg/m^2
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce topotecan dose to 0.75 mg/m^2
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue topotecan
[†] Febrile neutropenia is defined within the CTCAE as a disorder characterized by an ANC <1000/ mm^3 and a single temperature of >101 degrees F or a sustained degree of ≥ 100.4 degrees F for more than an hour.		

Table 6.1.1.4.1.B: Dose modifications for thrombocytopenia, 5-day Topotecan		
	Hematologic Event	Dose Modification
Initial Occurrence	Any occurrence of grade 4 thrombocytopenia (platelets < 25,000/ mm^3) or Severe bleeding	Reduce topotecan dose to 1 mg/m^2
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce topotecan dose to 0.75 mg/m^2
Third occurrence	If any of the above toxicities occur after initial dose reduction	Discontinue topotecan

If the criteria for topotecan administration are not met at the beginning of a new cycle, this cycle should be postponed, but not longer than 14 days, until the patient recovered. If the next treatment cycle is postponed by ≥7 days because of toxicity, a dose- reduction by one level applies. Patients who do not have hematologic recovery sufficient for treatment within 14 days should discontinue drug.

6.1.1.4.3 Hematologic toxicity

- Subsequent cycles of therapy (i.e. Day 1 treatment) will not begin until the ANC is ≥ 1500/ mm^3 and the platelet count is ≥ 100,000/ mm^3. Therapy will be delayed for a maximum of two weeks until these values are achieved. Patients who fail to recover adequate counts within a 14 day delay should discontinue drug. Dose- adjustments

because of hematological toxicities are made based on the most severe toxicity of the preceding infusion.

- For first occurrence of febrile neutropenia, and/or documented grade 4 neutropenia persisting ≥ 7 days, reduce chemotherapy by one dose level on subsequent cycles.

- For recurrent febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting ≥ 7 days (after initial dose reduction), add prophylactic growth factors as per ASCO and/or institutional guidelines (See 6.1.1.1).

- Patients with grade 4 thrombocytopenia will have a 1 level dose reduction.

- No more than two dose-reductions because of postponed treatment are permitted.

6.1.1.4.4 Non-hematologic toxicity

- Management of non-hematologic toxicities on the reference arm should be per institutional practice and guidelines *except* for hepatic toxicity as noted below. 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.A.

- Other Major Organ Toxicity (not evaluated as disease related): If the patient has any clinically significant non-hematological drug related toxicity CTCAE grade > 3, the patient should discontinue drug unless strong clinical benefit and discussion with the Study Chair.

- Dose modifications for alopecia, nausea, constipation, or electrolyte abnormalities are not recommended.

- If treatment is delayed for greater than 3 weeks due to a drug-related non-hematologic toxicity, the patient should discontinue drug therapy.

6.1.1.4.4.1 Modifications for renal toxicity

Creatinine clearance (Clcr) 20 to 39 mL/min reduce dose of topotecan to 0.75 mg/m^2 per dose. Insufficient data are available in patients with severe renal impairment (Clcr less than 20 mL/min) to provide a dosage recommendation for topotecan.

If Clcr less than 20 mL/min delay in subsequent therapy for a maximum of 2 weeks until Clcr is acceptable for treatment (≥ 20 mL/min). If no recovery after 14 days, patient should discontinue the drug.

6.1.1.4.4.2 Modifications for hepatic toxicity

Plasma clearance of topotecan in patients with hepatic impairment (serum bilirubin levels between

1.7 and 15.0 mg/dL) no dose adjustment is necessary (The half-life is increased slightly; usual doses are generally tolerated).

6.2 Arms II (cediranib and olaparib), III (cediranib alone), and IV (olaparib alone)

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.

Arm II

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	30 mg Monday through Friday (weekend off)
-2	20 mg daily
-3	20 mg Monday through Friday (weekend off)

For Arm II, 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 the 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 Study Chair**.

Arm III

Dose level	Cediranib tablets
1	30 mg daily
-1	30 mg Monday through Friday (weekend off)
-2	20 mg daily
-3	20 mg Monday through Friday (weekend off)

6.2.1 Hematologic toxicity

6.2.1.1 Use of hematopoietic agents

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.

Use of granulocyte-colongy stimulating factors will not be allowed in Arms II, III and IV.

6.2.1.2 Dose modifications

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

Table 6.2.1.2A: Dose Modification and Management of Hematologic Adverse Events, Arms II-IV

Hematologic Event	Dose Modification
Absolute neutrophil count ≥ 1500/mm^3 **AND** Platelets ≥ 100,000/mm^3 **AND** Hemoglobin ≥ 8 mg/dL	Maintain dose level
Absolute neutrophil count < 1500/mm^3 **OR** Platelets < 100,000/mm^3 **OR** Hemoglobin < 8 mg/dL	Hold treatment for up to 14 days until absolute neutrophil count ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, and hemoglobin ≥ 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, at the treating investigator's discretion. For patients whose treatment is held for ANC between 1000 and 1500/mm^3, 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 ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, and hemoglobin ≥ 8 mg/dL after 14 days

	should be removed from the study treatment.
Grade 4 hematologic AE related to cediranib or olaparib that does not resolve to absolute neutrophil count ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, and hemoglobin ≥ 8 mg/dL despite maximum supportive care after 14 days.	Discontinue study drug(s)

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.

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 Study Chair.

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 the 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 Study Chair.

6.2.2 Non-hematologic toxicity

Table 6.2.2.A: General Management of Non-Hematologic Toxicity, Arms II - IV

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
Any ≥ 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 ≤ 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, at the treating investigator's discretion[2]. The Study Chair should be informed regarding all dose modifications.
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 ≤ 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, at the treating investigator's discretion[2]. The Study Chair should be informed regarding all dose modifications. Patients whose

	toxicity has not resolved after 14 days will be removed from the study treatment.
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.	Discontinue study drug(s)
[1]**At the discretion of the investigator, one drug may be held or dose modified or discontinued independently if the observed toxicity is attributed to only one of the drugs, while the patient continued to receive the second 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.	

The management of general adverse events not otherwise specified in the following sections should be as per Table 6.2.2.A. Management of specific toxicities, including hypertension, diarrhea, proteinuria, decrease in LVEF, fever and neutropenia, nausea and vomiting, thyroid toxicities, reversible posterior leukoencephalopathy syndrome (RPLS) and gastrointestinal perforation should be as further outlined in the below specific subsections and not per Table 6.2.2.A.

* Management of olaparib-induced nausea and vomiting

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

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

6.2.2.1 Hypertension **(12/05/2016)**

Only doses of cediranib will be modified for hypertension; olaparib doses will not be reduced unless other toxicities are experienced.

Table 6.2.2.1.A: Hypertension Monitoring and Management

- See Appendix VI 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
- 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.
- **Note**: Stopping or reducing the dose of cediranib is expected to cause a decrease in BP. **The treating physician should monitor the patient for hypotension (also during the weekend when the patients do not take cediranib for DL-1 and DL-3) and adjust the number and dose of antihypertensive medications accordingly.**

Event	Definition	Antihypertensive Therapy	Blood Pressure Monitoring	Cediranib/ Dose Modification
Grade 1	Asymptomatic transient (<24 hours) increase by >20 mmHg diastolic or to ≥ 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 ≥ 140/90 mmHg if previously WNL Monotherapy may be indicated	Initiate BP medication for first line treatment. Suggestions: 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 "maximized" drug regimen, then add a second agent.	Increase frequency of monitoring until stabilized to BP <140/90 mmHg	Do not hold cediranib unless otherwise clinically necessary

		Study drug does not need to be held unless otherwise clinically necessary *Consider renal consult*		
Grade 3	Requiring more than one drug or more intensive therapy than previously.	Maximize 2 drug regimen • *Suggestions:* ACE-inhibitor + BB Escalate doses of existing medication until BP is controlled or at a maximum dose. If BP is not controlled to < 140/90 mmHg with two drug regimen, then add a third agent. **Study Drug will not be held during trial of multi- drug combinations. Additional anti-hypertensive drugs, up to a total of 4, may be maximized for blood pressure control.** *Consider consult with a blood pressure management specialist if greater than 3 drugs are required for BP control.*	Increase frequency of monitoring until stabilized to BP <140/90 mmHg	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). 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. If BP is reduced to Grade 1 within 14 days, cediranib may be resumed at prior dose.
Grade 4	If threatening consequences OR SBP ≥ 180mmHg OR DBP ≥ 110mmHg	Initiate treatment Hospitalize patient for ICU management, IV therapy as necessary 14 days are allowed to maximize the full effect of anti-hypertensive agents.	Intensive BP monitoring (hospitalization if necessary)	**Hold cediranib.** If BP is reduced to Grade 1 within 14 days, cediranib may be resumed at a reduced dose after discussion with the Study Chair and/or sponsor.

WNL, within normal limits

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 ≥1+ proteinuria 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**
Greater than 2+ on urine dipstick or U/A **AND** Creatinine ≤1.5x ULN	Perform UPC.	Continue study drugs at planned dose.
Greater than 2+ on urine dipstick or U/A **AND** Creatinine >1.5x ULN	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 6.2.2.3A		

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.
*Please consider requesting T3/T4 where TSH is elevated.	

6.2.2.5 Decrease in LVEF **(12/05/2016)**

Patients who have any of the following should undergo an echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan at baseline and every four cycles (16 weeks) while on study:

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- Prior central thoracic radiation therapy (RT), including RT to the heart

- 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:

Table 6.2.2.5.A: Management and Monitoring of Decreased LVEF

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 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cediranib and/or olaparib should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Cediranib and/or olaparib should be discontinued upon diagnosis of RPLS. 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. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents (12/05/2016)

Investigational Agents

The investigational agents administered in NRG-GY005 are:

Cediranib: NSC# 732208 Sponsor: DCTD, NCI

Olaparib: NSC# 747856 Sponsor: DCTD, NCI

For patients on Arms 2, 3, or 4 receiving Cediranib and/or Olaparib, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.5.2.2 of the protocol.

Commericial Agents

The commercial agents administered in NRG-GY005 are paclitaxel, topotecan, and PLD. For patients on Arm 1 receiving only commercial agents, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.5.2.1.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

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 CTEP Study Agents

7.3.1 Adverse Effects (01/17/2017)

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, 2018[1]

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		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis		***Anal mucositis (Gr 2)***
	Constipation		***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dysphagia		***Dysphagia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal perforation[3]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
		Pancreatitis	
	Rectal mucositis		***Rectal mucositis (Gr 2)***
	Small intestinal mucositis		***Small intestinal mucositis (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	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		***Thyroid stimulating hormone increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Generalized muscle weakness		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
	Lethargy		
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 4)***
	Vascular disorders - Other (hemorrhage)[5]		

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

[2]Gastrointestinal 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.

[3]Gastrointestinal 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.

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

[5]Hemorrhage 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
HEPATOBILIARY 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.

[1]

7.3.2 Adverse Effects (27-AUG-2021) (07.07.2023)

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 3449 patients.* Below is the CAEPR for Olaparib (AZD2281).

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

Version 2.6 June 5, 2023[1]

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
Abdominal pain			***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
	Urinary tract infection		
INVESTIGATIONS			
	Creatinine increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
		Platelet count decreased	
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	
VASCULAR DISORDERS			
		Vascular disorders - Other (venous thromboembolism)	

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

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

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

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Enterocolitis; Esophageal stenosis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Obstruction gastric; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fever; Malaise; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Dermatitis radiation; Fracture; Gastrointestinal anastomotic leak; Injury, poisoning and procedural complications - Other (vena cava injury); Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Hemoglobin increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Bone pain; Generalized muscle weakness; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain; Rotator cuff injury; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain

NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (decreased glomerular filtration rate); Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Pruritus
VASCULAR DISORDERS - Arterial thromboembolism; Flushing; Hot flashes; Hypertension; Hypotension; Peripheral ischemia; Thromboembolic event

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

7.4 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 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 Requirement, 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 CTEP at 301-230-0159 and NRG Regulatory Affairs by phone 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 **(12/05/2016)**

7.5.2.1 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:

- "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.

[1]Serious 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

7.5.2.2 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/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 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:

- "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.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

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

Expedited 24-hour notification followed by complete report within 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

7.5.3 Reporting to the Site IRB/REB

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

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.

7.5.5 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. REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

8.1 Investigator and Research Associate Registration with CTEP

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

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

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

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

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

8.1.2 **Site Registration Requirements (12/05/2016)**

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

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

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

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

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

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

8.1.2.1 Downloading Site Registration Documents:

Site registration forms may be downloaded from the NRG-GY005 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 ####
Click on the Site Registration Documents link

8.1.2.2 Site Specific Requirements for NRG-GY005 Site Registration:

- 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.

8.1.2.3 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 3000
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. The DTL application is located on the CTSU members' website at www.ctsu.org. Any individual at the

enrolling site on a participating roster may initiate the site DTL. Instructions on completing the DTL are embedded in the DTL application.

8.1.2.4 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 (12/05/2016)

- 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@nrgoncology.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 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.

8.1.3.2 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@nrgoncology.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

OPEN

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange.

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

OPEN User Requirements

OPEN users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients: Be on a Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type. A DTL is required for the study. The registrar(s) must also be assigned the OPEN Registrar task on the DTL.
- Have regulatory approval for the conduct of the study at their site.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form.

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 ctsucontact@westat.com.

* The standard time to begin therapy following registration is 2 weeks, however, this may be not done on the specific dates and times due to the following reasons, including but not limited to, delayed clinic schedule, incremental weather, or national holidays.

9.0 DRUG INFORMATION

9.1 Topotecan (NSC #609699)

9.1.1 Formulation:

Topotecan is a cell cycle specific inhibitor of the nuclear enzyme topoisomerase I. It has a mean half-life of approximately three hours. Topotecan's metabolism and clearance are complex but it is estimated that approximately 40% of the drug undergoes renal clearance.

9.1.2 Supplier/How Supplied:

Topotecan is commercially available and is supplied in a sterile form for intravenous use only.

- **Topotecan for Injection (lyophilized powder)** is available generically as a sterile, lyophilized, buffered, light yellow to greenish powder available in single use vials

containing topotecan hydrochloride equivalent to 4 mg of topotecan as the free base, with mannitol 48 mg and tartaric acid 20 mg. Hydrochloric acid and sodium hydroxide may be used to adjust the product pH. Available products do not contain an antimicrobial preservative; thus any unused product should be discarded within 24 hours of initial vial entry.

- **Topotecan Injection (solution)** is available generically in individually-packaged single-use vials containing a sterile, non-pyrogenic, clear, yellow to yellow-green solution of topotecan HCl equivalent to 4 mg of topotecan as the free-base at a concentration of 1 mg/mL.

9.1.3 Solution Preparation:

Topotecan for Injection (lyophilized powder) reconstitution:

- Reconstitute lyophilized topotecan HCl with 4 mL sterile Water for Injection, USP (SWFI), to produce a yellow to yellow-green solution with concentration equal to 1 mg/mL and a pH within the range, 2.5 – 3.5.
- Dilute an amount of drug appropriate for a patient's dose in 50 – 250 mL of either 0.9% Sodium Chloride Injection (0.9%NS) or 5% Dextrose Injection (D5W), USP.

Topotecan Injection (solution) reconstitution:

- Each milliliter of solution contains topotecan hydrochloride equivalent to 1 mg of topotecan (free base), with 5 mg tartaric acid, NF, and SWFI. Hydrochloric acid and/or sodium hydroxide may be added to adjust product pH within the range 2.6 – 3.2.
- Dilute an amount of Topotecan Injection (1 mg/mL) appropriate for a patient's dose in a minimum volume of 50 mL of either 0.9% Sodium Chloride Injection (0.9%NS) or 5% Dextrose Injection (D5W), USP.

9.1.4 Storage/Stability:

Topotecan for Injection (lyophilized powder) storage and stability:

• Store intact vials protected from light in the original cartons at controlled room temperature between 20° – 25°C (68° – 77°F).
• After reconstitution with SWFI, vials should be used immediately.
• After dilution with 0.9% NS or D5W, solutions prepared with Topotecan Injection are stable for at least 24 hours when stored at 20° – 25°C under ambient lighting conditions.

Topotecan Injection (solution) storage and stability:

- Store intact vials under refrigeration at 2° – 8°C (35.6° – 46.4°F) and protected from light in the original packaging carton.
- After dilution with 0.9% NS or D5W, solutions prepared with Topotecan Injection are stable for 24 hours when stored at 20° – 25°C (68° – 77°F) under ambient lighting.

9.1.5 Adverse effects:

Hematologic: thrombocytopenia, leukopenia, anemia, neutropenia
Gastrointestinal: nausea and vomiting, mucositis, diarrhea
Skin: rash
Other: alopecia, fever, flu-like symptoms

*Refer to Package Insert for additional information.

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/Stability
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.

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.

9.2.3 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 may be re-challenged with the drug. See section 6.1.1.2.2.2.

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

9.3 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:

9.3.1 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.

9.3.2 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.

9.3.3 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 in-line filter.

9.3.4 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.

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

9.3.6 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.

9.4 Cediranib (AZD2171)

9.4.1 Description

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

Other Names: Cediranib, AZD2171 maleate

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

Molecular Formula: $C_{25}H_{27}FN_4O_3 \cdot C_4H_4O_4$

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

Approximate Solubility: The aqueous solubility of Cediranib 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).

Mode of Action: Cediranib 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.

9.4.2 How Supplied

Astra-Zeneca supplies and CTEP, NCI, DCTD distributes Cediranib. The agent is available as beige film-coated tablets containing 15 mg, and 20 mg of Cediranib 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.

9.4.3 Storage and stability

Storage: Store intact bottles at controlled room temperature [20°C-25°C, (68-77°F)].

Stability: Stability studies are ongoing. Dispense AZD2171 (cediranib) 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 AZD2171 (cediranib) 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. **(12/05/2016)**

9.4.4 Route of Administration

Oral. Cediranib tablets should be taken either one hour before or two hours after meals.

9.4.5 Potential Drug Interactions **(12/05/2016)**

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 α1-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.

9.4.6 Patient Care Implications

Agents that inhibit VEGF signaling have the potential to affect wound healing; therefore, it is recommended that cediranib 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 cediranib 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.

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.

9.4.7 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.
Cediranib is an investigational agent and will be supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Cediranib is provided to the NCI under a Collaborative Agreement between AstraZeneca International and the DCTD, NCI (see Appendix I).

9.4.8 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, 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 participating investigator at that institution.

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, a "current" password, and active person registration status. 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.

9.4.9 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.

9.4.10 Investigator Brochure Availability **(12/05/2016)**

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

9.4.11 Destruction and Return

Standard NCI return procedures will be followed.

9.4.12 See Section 7.3.1 for the Cediranib CAEPR

9.4.13 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application:

https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.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)

9.5 Olaparib (AZD2281, NSC 747856, Lynparza™)

9.5.1 Description

Chemical Name: 4-[3-(Cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluro- benzyl]-2-H-phthalazin-1-one

Other Names: AZD2281, KU-0059436; CO-CE 42; PARPi; Olaparib, Lynparza™

CAS Registry Number: 763113-22-0

Molecular Formula: $C_{24}H_{23}FN_4O_3$

Molecular Weight: 434.47

Approximate Solubility: Olaparib is freely soluble in dimethylsulphoxide (DMSO) and 1-methyl-2-pyrrolidinone (NMP), sparingly soluble in ethanol and methanol, and only very slightly soluble in water (<0.25 mg/mL).

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.

9.5.2 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.

9.5.3 Storage and stability

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.

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 PMBAfterHours@mail.nih.gov for determination of suitability

9.5.4 Route of Administration **(12/05/2016)**

Oral. Olaparib tablets can be taken by mouth.

9.5.5 Potential Drug Interactions **(12/05/2016X)**

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.

9.5.6 Patient Care Implications **(12/05/2016)**

Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should agree to use two (2) highly effective forms of contraception throughout study participation and for at least one (1) month after the last dose of olaparib. Male study participants should avoid fathering a child or donating sperm during the study and for three (3) months after the last dose of olaparib. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

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.

9.5.7 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 will be supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

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

9.5.8 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, 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 participating investigator at that institution.

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, a "current" password, and active person registration status. 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.

9.5.9 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.

9.5.10 Invesitgator Brochure Availability **(12/05/2016)**

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

9.5.11 Destruction and Return

Standard NCI return procedures will be followed.

9.5.12 See Section 7.3.2 for the Olaparib CAEPR

9.5.13 Useful Links and Contacts **(12/05/2016)**

- 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 IB Coordinator: IBcoordinator@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 Blood Pressure Cuffs (12/05/2016)

A patient who is randomized to a study group 2 or 3 will be given a blood pressure cuff. Blood pressure cuffs that are supplied for this study, are only to be used for this study.

9.6.1 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.

9.6.2 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. PATHOLOGY

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

11. 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 (12/05/2016)
Specimens listed below should not be submitted until after patient registration and Bank ID assignment.

Sites in Korea: Please refer to Appendix XIV for biospecimen requirements and procedures. Some of the biospecimens included in the tables below are not applicable for sites in Korea.

11.2.1.1 Integrated Biomarker Specimen Requirements (12/05/2016)
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, 7] 8mL drawn into CPT (citrate) tube	Prior to study treatment	Preclinical Development Research Core (PDRC) **the day the specimen is collected**[2]
CEC C1D3 Whole Blood (WB03)[1, 7] 8mL drawn into CPT (citrate) tube	Cycle 1, day 3 of study treatment, **only if WB02 was submitted**	
BROCA-HR Whole Blood (WB01)8 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 *Submit one - FP02 is preferred; Submit FM02 only if FP02 is not available*	NRG BB-Columbus within 2 weeks of registration[3]
BROCA-HR FFPE Metastatic Tumor (FM02)[4] 2 unstained slides (charged, 10µm)[5]		

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]
ALL PATIENTS RECEIVING OLAPARIB (ARMS 2 and 4) – PHASE II PORTION ONLY		
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 of 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 (ARMS 2 and 3) – PHASE II PORTION ONLY		
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 of 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	

1 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 that the day indicated by the specimen collection time point.

2 Preclinical Dveleopment 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. 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.

3 NRG BB-Columbus / Protocol NRG GY005, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org.

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

5 If patient consents to the optional FFPE collection (FP01/FM01; section 11.2.1.2) and a block will be submitted on a permanent basis to fulfill both the mandatory (FP02/FM02; section 11.2.1.1) and optional (FP01/FM01; section 11.2.1.2) specimen requirements, then label the block FP01 (for primary) or FM01 (for metastatic). Complete and ship both the FP01 and FP02 (for primary) or FM01 and FM02 (for metastatic) specimen transmittal forms (i.e., Form TR) with the block.

6 Do not use glass blood collection tubes.

7 Sites in Japan and Korea should not collect CEC whole blood biospecimens.

8 Sites in Korea should not collect BROCA-HR whole blood biopspecimens.

11.2.1.2 Exploratory Biomarker Specimen Requirements

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 *(Preferred FFPE)*	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 *(Optional if FP01, FRP01, or FRM01 is submitted)*	
FFPE Recurrent Primary Tumor (FRP01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, or FRM01 is submitted)*	
FFPE Recurrent Metastatic Tumor (FRM01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, or FRP01 is submitted)*	
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[1]
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	
Research Final Plasma (PB11) prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)	At disease progression or end of treatment	NRG BB-Columbus within 26 weeks of registration[1]

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

1 If patient consents to the optional FFPE collection (FP01/FM01; section 11.2.1.2) and a block will be submitted on a permanent basis to fulfill both the mandatory (FP02/FM02; section 11.2.1.1) and optional (FP01/FM01; section 11.2.1.2) specimen requirements, then label the block FP01 (for primary) or FM01 (for metastatic). Complete and ship both the FP01 and FP02 (for primary) or FM01 and FM02 (for metastatic) 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

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

11.2.3 Laboratory Testing

Assay details are included in Appendix VIII.

11.2.3.1 Circulating Endothelial Cells (Integrated Biomarker) (12/05/2016)

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 12C208
10 Center Dr, Bethesda, MD 20892
Phone: 240-760-6330
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) (12/05/2016)

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.

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) (12/05/2016)

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 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.

11.2.3.5 Plasma Angiome (Exploratory 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.

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.

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.

11.2.4 Banking Specimens for Future Research

Details regarding the banking and use of specimens for future research can be found in Appendix VII.

11.3 Quality of Life/ Patient Reported Outcomes

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 Phase II and III trials and has a specified analysis plan. All other endpoints (NFOSI-18 TSE, NFOSI-18 F/WB, NTX-4, EQ-5D) are exploratory PRO endpoints for the Phase III studies and will be analyzed post-hoc (see Appendix IX).

The following PRO assessments will be performed every 12 weeks for 2 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. (exploratory secondary): PRO: NFOSI-18 TSE
3. (exploratory secondary): PRO: NFOSI-18 F/WB
4. (exploratory secondary): PRO: NTX-4
5. (exploratory secondary): EQ5D

Disease-related Symptom-Physical (DRS-P)
This 9-item scale, the first 9 items of the NFOSI-18, 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 et al., 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. We propose the targeted 9-item DRS-P subscale as the main (*secondary*) PRO endpoint. Of note, after establishing that these 9 questions are the most important disease-related symptoms to women with ovarian cancer (Jensen et al., 2011), we further evaluated and demonstrated through cognitive debriefing interviews with 18 women with ovarian cancer, that these items are understood as intended.

Exploratory endpoints: TSE, Ntx-4, F/WB, EQ-5D. These endpoints will be included according to the schedule detailed below (Table 4). Platinum-based chemotherapies may cause neuropathy. The NTX-4 has been developed to assess neuropathy in cancer patients undergoing chemotherapy. Both of these scales are part of the FACIT arsenal of quality of life and symptom scales which are available in multiple languages. The EQ5D is a five-item instrument that offers a validated method of deriving utilities for use in CEA.

a. **Treatment side effects (TSE) and function/well-being (F/WB**) from the NFOSI-18 will be secondary PRO endpoints. As the TSE scale is not intended to cover all, or even most, of the anticipated side effects across these two trials, we propose to use the single summary TSE item ("I am bothered by side effects of treatment") as the unit of analysis comparing overall side effect bother of the treatment arms. There is precedent for this (Cella et al., 2013). The EQ5D will be included to estimate a single index value for health status.

Table 11.1 Study calendar for PRO

	Pre-Treatment	During planned treatment*		Following planned treatment*		Post-Treatment*
Quality of Life & Comparative Effectiveness Parameters	Prior to Initial Study Treatment	Week 12 (or prior to cycle 4)	Week 24 (or post cycle 6)	Week 36	Week 48	Every 3 months for 2 years for platinum-resistant
PRO: DRS-9	X	X	X	X	X	X
PRO: TSE	X	X	X	X	X	X
PRO: F/WB	X	X	X	X	X	X
PRO: Ntx-4	X	X	X	X	X	X
EQ5D	X	X	X	X	X	X

QOL Data compliance.
In GY005, similar to other trials with very advanced disease populations, the compliance challenge will occur because of the relatively short intervals of PFS and OS. In the platinum-resistant population, the median PFS is 12 weeks and the median OS is less than one year. Our QOL non-compliance is highest among those patients who have stopped study treatment for either progression or adverse events. Importantly, these two reasons do not obviate the need for the research nurses and clinical research associates to continue to collect QOL data as scheduled. It is frequently the case, under these scenarios, that an institutions' research team assumes that if the patient is off of the clinical trial, that she is also finished with her QOL assessments. These "institutional errors" can be remedied by diligent educational efforts and frequent reminders for follow-up, even if the patient is "off study." We are mindful of the fact that even with progressing disease, patients appreciate being asked about their health and well-being, and are compliant with completing the questionnaires. This is especially true for the ovarian cancer patient population. It is worth noting that in previous ovarian trials (e.g., 24 months follow-up) we achieved close to 80% compliance. See Appendix X for the details of NRG's strategies to optimize QOL long-term compliance with data reporting.

12. 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://ctepcore.nci.nih.gov/iam/) 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 ctsucontact@westat.com.

NRG Data Management Forms

The following forms must be completed and submitted to the NRG Statistical and Data Management Center—Buffalo Office (SDMC) in accordance with the schedule below. NRG electronic case report forms must be submitted through the Medidata Rave Electronic Data Entry System (www.imedidata.com). All amendments to forms must also be submitted through Medidata Rave. The pathology reports can be sent to the NRG SDMC via postal mail or uploaded in Medidata Rave. The upload option is an alternative method for submitting paper reports.

Form	Comments
Baseline Folder ***(Forms due within 2 weeks of registration)***	
Baseline/History Forms: - Visit Information- Baseline Form - Registration Form - Pre-Treatment Summary Form - Pre-Study History Information - Pre-Study History Primary Surgery - Pre-Study History Chemotherapy - Pre-Study Radiation Therapy Information - Specimen Consent - ECHO/MUGA Form - ECG Information Form - Concomitant Medications Form - Vitals Form - Biomarker Information Form - Medical History Form - BRCA Status Form - Specimen Consent	The appropriate forms will load in baseline folder based on answers reported on the corresponding Baseline Visit Information form.

Visit Folder ***(Forms due with in 2 weeks of completion of each cycle)***	
Cycle Information and Treatment Forms: - Visit Information Form - Cycle Drug Information Form - Labs and Chemistries Form - Vitals Form - ECHO/MUGA Form - ECG Information Form - Concomitant Medications Form - Biomarker Information Form Toxicity (Adverse Event) forms: - Section 1 Form - Adverse Event Form - Adverse Event Grades	The appropriate forms will load in folder based on answers reported on the corresponding Visit Information form.
Solid Tumor Evaluation Folder	
Solid Tumor Evaluation Forms: - Tumor Assessment Visit Form - Target Lesions Form - Non-Target Lesions Form - No Target Lesions Form - New Target Lesions Form - Status and Response Form	The appropriate forms will load in folder based on answers reported on the corresponding Tumor Assessment Visit Form.
Pathology Folder	
- Pathology Report for Primary Disease - Pathology Report for Recurrent Disease	Upload the reports online in Medidata Rave or submit via postal mail to the address below: NRG Oncology Statistics and Data Management Center Roswell Park Cancer Institute Elm and Carlton Streets Buffalo, NY 14263

Quality of Life Folder	
Patient Reported Outcome Forms (QOL Scantron): - Scantron: Prior to study therapy - Scantron: 12, 24, 36, 48, 60, 72, 84, 96, and 108 weeks after starting study therapy - PRO/QOL Contact Information - Patient Reported Outcomes Schedule	Please mail the original QOL Scantron forms to the address below: NRG Oncology Statistics and Data Management Center Roswell Park Cancer Institute Elm and Carlton Streets Buffalo, NY 14263 Please note: QOL Scantron form must be ordered from the NRG Buffalo SDMC by submitting the Scantron Order Form posted on the CTSU website.
Translational Research Folder	
TR Forms: - CEC Pre-treatment Whole Blood (WB02) - CEC C1D3 Whole Blood (WB03) - BROCA-HR Whole Blood (WB01) - BROCA-HR FFPE Primary Tumor (FP02) *FP02 or FM02 must be submitted** - BROCA-HR FFPE Metastatic Tumor (FM02) *FP02 or FM02 must be submitted** - Future Use Whole Blood (WB04) - FFPE Primary Tumor (FP01) - FFPE Metastatic Tumor (FM01) *optional* - FFPE Recurrent Primary Tumor (FRP01) *optional* - FFPE Recurrent Metastatic Tumor (FRM01) *optional* - Research Pre-treatment Plasma (PB09) - Research C2D1 Plasma (PB10) - Research Final Plasma (PB11)	The appropriate forms will load in the Translational Research Folder based on the answers reported on the Specimen Consent form. An electronically completed copy of Form TR must accompany each specimen shipped. Handwritten forms will not be accepted. WB01-WB03 are due 1 week from registration. FP02 and FM02 are due 2 weeks from registration. **If patient consents to the optional FFPE collection (FP01/FM01; section 11.2.1.2) and a block will be submitted on a permanent basis to fulfill both the mandatory (FP02/FM02; section 11.2.1.1) and optional (FP01/FM01; section 11.2.1.2) specimen requirements, then label the block FP01 (for primary) or FM01 (for metastatic). Complete and ship both the FP01 and FP02 (for primary) or FM01 and FM02 (for metastatic) specimen transmittal forms (i.e., Form TR) with the block.* WB04 is due 2 weeks from registration. FP01, FM01, FRP01, and FRM01 are due 8 weeks from registration. PB09-PB11 are due 5 weeks from registration.
Treatment Completion Folder ***(Forms due within 2 weeks of Treatment Completion)***	

- Treatment Completion Form	Please submit the Treatment Completion Form after all protocol directed therapy has been discontinued.
Follow-up Visit Folder ***(Forms due within 2 weeks of follow-up visits, disease progression or death)***	
Visit Information Follow-Up Form Follow-up Form Concomitant Medications Form Labs and Chemistries Form Biomarker Information Form Non-Protocol Therapy Form. Follow-Up Adverse Event Reporting: - Part 1 Form - Terms Form - AE Grades Form	The appropriate forms will load in folder based on answers reported on the corresponding Visit Information form.
Source Documentation Upload Folder	
- Source Documentation Upload Form - SDV Baseline - Source Documentation Upload Form – Visit 1 - Source Documentation Upload Form – Visit 2	A source documentation review will be conducted for the first two patients enrolled from each site (as identified by a unique NCI identifier). The review will require that source documentation be uploaded in Medidata Rave for eligibility, baseline, and the first two cycles of treatment. Please see Appendix XI: Protocol Monitoring Plan for details.

Summary of Data Submission
Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting.

For reporting of secondary cancers or other report forms available in Rave:
Indicate form for reporting in Rave, timeframes, add if loading of the pathology report is required.

Global Reporting/Monitoring
This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

Phase II accrual was suspended on June 16, 2017. At the interim analysis in July 2018, the Data Monitoring Committee voted to drop the single-agent olaparib arm. The Phase III trial will be continued with 3 arms: standard chemotherapy, cediranib+olaparib, and cediranib alone. Phase II patients randomized to these three arms will be included in the Phase III trial accrual targets, and will be included in the primary analysis according to their randomized treatment assignment. For clarity, references to the single-agent olaparib arm have been removed from the Phase III statistical methods sections.

13.1.1 Endpoints.

Phase II Study (06-AUG-2021)
Primary efficacy endpoint: Progression-Free Survival (PFS), defined as the time from study enrollment to the onset of progression as determined by RECIST v1.1 criteria, or death due to any cause, whichever occurs first. For individuals who are alive and progression-free the time at risk will be defined as the time from the study enrollment date to the date of the last disease assessment.

Secondary endpoints:
a. Secondary efficacy endpoint: Objective response rate (ORR, either partial or complete response) defined by RECIST v1.1 criteria, in the setting of recurrent platinum-resistant or refractory ovarian, primary peritoneal, or fallopian tube cancer.
b. Safety endpoint: safety as measured by frequency and severity of adverse events by Common Terminology Criteria for Adverse Events (CTCAE).

The median PFS reported in studies with the single agent standard chemotherapy in women with recurrent platinum-resistant or refractory ovarian cancer ranges between 3 months to 4 months. The primary analysis of PFS will be assessed using a proportional hazards model with patients analyzed according to the arm to which they were randomized, regardless of whether treatment is received.

To allow for a better understanding of time to subsequent therapy and OS, patients on experimental study drug(s) or standard chemotherapy arm will be followed after progression, 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.

Phase III Study (06-AUG-2021)
Primary efficacy endpoint: The durations of PFS and overall survival (OS) are co-primary endpoints in the phase III component of this study.

OS is defined as the time from study enrollment to death due to any cause. For those individuals, who have no death reported at the time of the analysis, the time at risk of death will be assessed from the date of study enrollment to the date that the patient was last known to be alive. The

expected median time to death for this patient population receiving standard treatment is 15 months.

For the end of the Phase III primary analysis, Progression-Free Survival (PFS) is defined as the time from study enrollment to the onset of progression as determined by RECIST v1.1 criteria, or death due to any cause, whichever occurs first. PFS censoring rules for the primary analysis, and sensitivity analyses for the PFS endpoint, are provided in Section 15.1.6.

Secondary endpoints:
a. Secondary efficacy endpoint: ORR.
b. Safety endpoints: frequency and severity of adverse effects as defined by CTCAE.

Objective with Integrated Biomarkers

a. To 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 combination, compared to standard chemotherapy, in the setting of recurrent platinum-resistant or-refractory ovarian, primary peritoneal or fallopian tube cancer.

13.1.2 Randomization Procedure. **(06-AUG-2021)**
The treatment allocation procedure will allocate a nearly equal number of patients to each available study regimen. Randomization will be stratified by the following factors:

1) Receipt of prior bevacizumab (yes vs no),

2) Prior platinum free interval (resistant vs. refractory disease)

a) Resistant disease: progression within 6-months of receiving the last course of platinum therapy.
b) Refractory disease: progression while receiving platinum.

To balance the treatments assigned to Japanese and Korean patients, the randomization will be stratified by Country of Treatment. The country of Treatment will be determined by the NRG institution number and will have three levels: (1) Japan, (2) Korea, and (3) Other. The country of treatment stratification factor will not be included in the statistical analyses. It serves administrative purposes only.

The Country of Treatment stratification was incorporated in the Phase III randomization scheme. It was not used during Phase II.

Japanese Cohort Accrual. **(06-AUG-2021)**

Accrual to the Japanese cohort will remain open until about three months before the data cutoff or until 24 Japanese patients have enrolled, whichever occurs first. These patients will follow the same study plan and procedures as patients recruited to the primary cohort.

To help clarify the analysis plans, the following cohorts are defined.

Cohort Label	Description
Primary Cohort	Includes the 510 patients enrolled during the global accrual period. Four patients from Japan are included in this cohort. The primary cohort will be considered mature when 137 deaths have been observed among patients randomized to the chemotherapy arm in this cohort (i.e. the data cutoff). See Section 13.1.4.
Japanese Cohort	Includes all Japanese patients enrolled before the primary analysis data cutoff. This cohort is expected to have up to 24 patients; four accrued to the primary cohort, and up to another 20 between the suspension of accrual to the primary cohort and the primary analysis data cutoff date. Analyses of the Japanese cohort may be performed when maturity in the Japanese cohort is similar to that of the primary cohort to allow for sufficient follow up within the Japanese cohort.

All planned analyses described below relate to the primary cohort unless otherwise stated.

13.1.3 Sample size with power justification.

Phase II Study (06-AUG-2021)
The target enrollment for the phase II component of the study is at least 52 patients randomized to each study regimen (approximately 208 patients). The randomization process will not be constrained to enroll only 52 patients in each regimen. In other words, the random allocation of study treatments to each patient will always have a stochastic component. Once the targeted number of patients has been enrolled, enrollment will be suspended to permit the PFS data to mature for the post-phase II analysis. The purpose of these analyses is to drop regimens that have insufficient evidence of activity to warrant further phase III evaluation at this time.

The expected monthly accrual rate for this study is 10.6 patients and enrollment onto the phase II component of this study is expected to require approximately 1.6 years after a brief initial startup period.

Comparison of experimental regimens to the standard chemotherapy regimen with regard to PFS:
When at least 164 of the patients enrolled in the study have either progression or death reported, the relative PFS event rate for each of the single-agent experimental regimens will be compared to the standard chemotherapy regimen. A proportional hazards model will be used to estimate the relative hazards in which the stratification factors that were used for treatment randomization (see Section 13.1.2) will be included as model covariates (including these covariates in the PH

model as stratification factors may create some strata with too few events at this point in the study to be included in the estimate of some hazard ratios). Those single agent experimental regimens that exhibit at least a 17% reduction in the estimated PFS event rate (compared to standard chemotherapy) at this time will be considered sufficiently active to warrant further evaluation in the phase III component of this study. If an experimental regimen truly reduces the instantaneous PFS event rate by 37.5%, then there is a 90% chance that the regimen will advance to the phase III component of the study. However, if the true PFS event rate for an experimental regimen is equivalent to standard chemotherapy, then there is an 80% chance that this regimen will be dropped following the phase III component of the study based on this criterion.

If there is sufficient evidence for at least one of the single-agent experimental regimens to proceed to the phase III component of this study, then the experimental combination regimen will be compared to the experimental single-agent regimen with the lowest PFS event rate. If the estimated PFS event rate among those randomized to the experimental combination regimen is lower than the single-agent regimen with the lowest PFS event rate, then the combination regimen will be considered to have sufficient activity to warrant further evaluation in the phase III component of the study.

If neither of the single-agent experimental regimens demonstrates at least a 17% reduction in the PFS event rate, but the combination regimen does demonstrate at least a 17% reduction in the PFS event rate, then the combination regimen will be considered sufficiently active to warrant further evaluation in the phase III component of the study.

Phase III Study (06-AUG-2021)

The phase III component of this study includes the standard of care chemotherapy, single-agent cediranib, and the combination of cediranib/olaparib treatment arms. The target sample size for the final analysis is 510 patients, with 170 patients randomized to the standard chemotherapy regimen (including those randomized during the phase II trial) and nearly an equal number of patients enrolled in each experimental regimen selected for phase III evaluation. When accrual is complete, at least 562 patients will have enrolled in the study, including 52 Phase II patients from the Olaparib only arm who will not be included in the final analysis. The expected monthly accrual rate is 10.6 patients. Enrollment onto the phase III component is expected to require about 2.7 additional years.

Notation for Study Hypotheses

Denote each of the study's null hypotheses as $H_{x,y}$ (H' for alternative hypotheses) in which the first subscript indicates the endpoint and the second subscript indicates the treatment pair being compared. Treatments will be denoted as: R for the reference regimen (chemotherapy), C for single-agent cediranib and C+O for the cediranib and olaparib combination. For instance, $H_{PFS,C:R}$ will denote the null hypothesis that the PFS event rates on single-agent cediranib and the reference regimen are equivalent.

Overview of Hypothesis Testing Strategy

This study involves two families of hypotheses to evaluate treatment efficacy. The null hypotheses in the first family of hypotheses are: $H_{PFS,C:R}$, $H_{PFS,C+O:R}$, $H_{OS,C:R}$, $H_{OS,C+O:R}$. These

null hypotheses assert that the experimental arm PFS event and death rates are equal to these rates on the reference regimen (chemotherapy) in women with recurrent platinum-resistant or -refractory ovarian, primary peritoneal or fallopian tube cancer. The strategy for controlling type I error across this family of hypotheses involves Bonferroni correction and hierarchical testing procedures, which are intended to strongly limit type I error to 0.025 (1-tail) for the entire first family of hypotheses.

Finally, if the experimental combination regimen is declared superior to chemotherapy and the single-agent cedirinib regimen is selected following the phase II component, a second family of hypotheses ($H_{PFS,C+O:C}$, $H_{OS,C+O:C}$) comparing the combination and single-agent cediranib will be evaluated for a 2-tail test.

Hypothesis Testing Procedures

Comparing the experimental regimens to the standard chemotherapy regimen with regard to PFS and OS (1st family of hypotheses):
The first family of hypotheses involves comparing each of the experimental regimens selected from the phase II component of this study to the reference group with regard to PFS and OS. To limit the overall type I error for this family of hypotheses, the type I error allocated to each of the first three hypotheses ($H_{PFS,C:R}$, $H_{PFS,O:R}$, $H_{PFS,C+O:R}$) will be 0.0083 (=0.025/3, 1-tail). This type I error will not be redistributed among these hypotheses, even though the $H_{PFS,O:R}$ test will not be considered in the Phase III study. A hypothesis from the second set of hypotheses ($H_{OS,C:R}$, $H_{OS,O:R}$, $H_{OS,C+O:R}$) will be tested, if and only if, the hypothesis concerning PFS with the same pair of treatment is rejected. For instance, $H_{OS,C:R}$ will be tested only if $H_{PFS,C:R}$ is first rejected. The type I error for each of these tests will also be 0.0083, when testing is appropriate.

The study will be considered sufficiently mature for this family of tests when there are at least 137 deaths reported among patients randomized to the standard chemotherapy regimen. If an experimental regimen truly reduces the death rate by 37.5%, then the expected number of deaths at that time in that treatment group is 110. This sample size provides nominal 90% power (provided the corresponding PFS hypothesis has already been rejected) for each of the pair-wise comparisons when the experimental regimen truly reduces the death rate 37.5% (OS hazard ratio (HR)=0.625) relative to the standard chemotherapy. This hazard ratio is comparable to increasing the median duration of survival by 9 months. The actual number of PFS events available at that time for each treatment-PFS comparison is random. Assuming 95% of the patients involved in the phase III component of this study have progressed or died when survival has sufficiently matured for these hypotheses, then there is 96% power if the experimental regimen decreases the PFS event rate 37.5% (PFS HR=0.625). This is comparable to increasing the median duration of PFS by 2-2.5 months.

Comparing the experimental combination regimen to the single-agent cediranib with regard to PFS and OS (2nd family of hypotheses):
If the experimental combination regimen demonstrates superiority to the standard chemotherapy regimen with regard to OS ($H_{OS,C+O:R}$ is rejected), then the experimental combination will be compared to single-agent cediranib. The type I error for this test will be 0.025 (2-tail). The study

will be considered sufficiently mature when there are at least 227 total deaths reported among those patients who were randomized to either the experimental combination regimen or single-agent cediranib. The power estimate of this test is complicated, since it not only depends on the true death rates of the two regimens being directly compared, but also the single-agent olaparib arm that is only implicitly involved in this comparison.

Likewise, if $H_{PFS,C+O:R}$ is rejected, the $H_{PFS,C+O:C}$ test will be conducted. The type I error for this test will be 0.025 (2-tail).

13.1.4 Analysis plan including plans for formal interim analysis.

Phase II study: (06-AUG-2021)
A single proportional hazards model (Cox 1972), which includes all four treatment groups with indicator covariates for the stratification factors used in the randomization procedure (see Section 13.1.2). This model will be used to estimate the hazard ratios for each of the experimental regimens relative to the chemotherapy group. This model will group patients by their randomized study regimen. All enrolled patients will be included in this analysis, regardless of their eligibility or compliance with their assigned study regimen.

Consideration will be given to stopping enrollment onto any particular experimental regimen if there are no clinical responses (complete or partial response) among the first 20 patients who are randomized to the regimen (during the phase II component) and at least initiate their assigned study treatment.

Phase III study:

A stratified logrank test will be performed for each hypothesis, when hypothesis testing is appropriate. The logrank tests will involve only those treatments that were selected at the end of the phase II trial and all of the patients who were randomized to these treatment groups regardless of whether they were enrolled during the phase II or phase III component of the study. Patients will be grouped by their randomly assigned treatment and will be included in the analysis regardless of their compliance with their assigned study treatment. The logrank procedures will be stratified by the factors used to balance the treatments during randomization (see Section 13.1.2).

Interim Analysis Plans: **(06-AUG-2021)**

The interim analysis will include an assessment of both futility and superiority. A planned interim analysis will be performed when at least half of the number of deaths (137/2≈69) required for the final analysis of the 1st family of hypotheses has occurred among those patients in the reference group. Due to the complexity of this study design, the interim analyses will follow proposed recommendations for simplifying interim monitoring guidelines (Freidlin et al 1999). If any of the null hypotheses $H_{PFS,C:R}$ or $H_{PFS,C+O:R}$ is rejected at $p \leq 0.0002$ (1-tail) at the time of the interim analysis then the corresponding hypothesis involving the same treatments, $H_{OS,C:R}$ or $H_{OS,C+O:R}$ will be assessed. If each of the hypotheses concerning PFS and OS can be rejected at $p<0.0002$ for any specified experimental regimen, then consideration will be given to

stop allocating the reference regimen to enrolling patients. While amending the randomization procedure this way would require making some information from the interim analysis public, the Data Monitoring Committee will also consider separately whether to publically releasing detailed results of the interim analysis.

On the other hand, if the conditional power under the alternative hypotheses (HR=0.625) for $H_{PFS,C:R}$ or $H_{PFS,C+O:R}$ is less than 0.40 at the time of the interim analysis then consideration will be given to stop enrolling patients onto the indicated experimental regimen and concluding that it is unlikely to be superior to the reference regimens.

The interim analysis will also include estimates of the hazard ratios and the corresponding confidence intervals for each of the experimental regimens relative to the reference regimens.

The results of interim analyses are reviewed by the NRG Data Monitoring Committee (DMC). The dates for the DMC's meetings are administratively scheduled without knowing the study results. Approximately eight weeks before its regularly scheduled meetings, the database is locked 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 upcoming meeting. The actual decision to terminate accrual or to release study results includes consideration of toxicities, treatment compliance, as well as results from external studies.

Japanese Cohort Analysis Plan: **(06-AUG-2021)**

At the data cutoff, the OS/PFS endpoints among the Japanese Cohort (defined above) will not be mature. Analyses of the Japanese cohort may be performed when maturity in the Japanese cohort is similar to that of the primary analysis in the Primary Cohort to allow for sufficient follow up within the Japanese cohort. This is expected about 24 months after the last Japanese patient enrolls. After the data are cleaned, an updated dataset will be provided to support other analyses among the Japanese cohort. Where data permit, summaries and analysis of primary and secondary efficacy endpoints will be performed for the Japanese cohort.

13.2 Statistical design for each correlative study

13.2.1 Patient reported outcome (PRO)

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 (DRS) among the study treatments. The primary measure for symptoms is the NFOSI-DRS-P, which is a 9-item PRO. The DRS-P score for the i^{th} patient-assessment is calculated as

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

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 jth 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 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.

A mixed-effects model will be used to estimate and compare the mean 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 DRS-P score, and assessment time. The primary analyses will include only those treatments selected at the end of the phase II study and all of the patients assigned to one of these treatments during either the phase II or phase III component of the study regardless of their compliance with the study treatment or eligibility status, provided at least one baseline (pre-treatment) and one follow-up assessment is available. For the primary analysis, patients will be grouped by their randomly assigned study treatment.

First, a mixed model will be used to conduct an omnibus test (across time) that compares the DRS-P scores from each experimental treatment group to the reference group. If an omnibus hypothesis is rejected then comparisons (between the particular experimental group and the reference group) at individual assessment-times will also be conducted. In order to control type I error, for treatment comparisons with regard to the DRS-P, the overall type I error for comparing each of the 3 experimenal regimens to the chemotherapy regimen will be limited to 0.0166 (0.05/3, 2-sided). The type I error will not be reallocated in the event that fewer than 3 experimental arms are selected following the phase II component of the study.

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 DRS-P are approximately 51.6 and 10.7, respectively. The primary analysis of DRS-P will focus on the assessments scheduled during the first year following enrollment onto the study. For the purposes of estimating power, it is assumed that there will be a 10% attrition of patients at the first reassessment time and 15% at each subsequent 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 the power to detect a constant 3.5 unit difference between treatment groups is approximately 85%. Alternatively, if the difference in DRS-P scores between treatment groups increases from 0 to 6.5 units over the first year, then this study has 82% power. If the null hypothesis concerning the equality of the mean DRS-P scores between an experimental regimen and chemotherapy is rejected, then a treatment-by-time interaction term will be added to the model in order to estimate temporal trends in the differences between these treatment groups.

Other PRO Scales

Each of the other general PRO scales will be analyzed with mixed models using procedures similar to those described above for the DRS-P. However, the scores from some PRO scales that are designed to assess very specific symptoms, like the NTX-4, usually involve a large number of individuals who report no such symptom, but a subset of patients will report significant symptoms (ie data exhibit clumping of scores at zero). In this case, a mixed-effect mixed-distribution (MEMD) (Berk et al, 2003) model will be used to estimate symptom scores. This model includes two components. One component involves a logistic model to estimate the probability of a nonzero score, and the second component models the mean of the nonzero scores. This model also incorporates random effects to account for repeated measures provided by each individual and permits specification of a correlation structure between the random effects for the two components of the model. This model also permits the inclusion of individuals with some missing follow-up observations.

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 Centered Outcomes Research 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.

13.2.2 Translational Research Studies

13.2.2.1 BROCA-HR

The hypothesis for this objective is that cancer cells need to be not only deficient in HR but also proficient in the alternative (error-prone) NHEJ DNA repair pathway to be sensitive to a PARPi. The BROCA-HR assay identifies mutations in genes that are involved in HR or NHEJ as well as the presence of several clinically relevant SNPs (See Section 2.4.1). While the 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 proportional hazards model (Cox, 1972) will be used to estimate the treatment hazard ratios (and variances) for each of the experimental treatments selected for phase III evaluation relative to the reference treatment (chemotherapy) group. All of the patients with BROCA-HR scores who were assigned to one of these treatments during either the phase II or phase III component of this study will be included in the analysis. The model will include adjustments for prior platinum-free interval, prior bevacizumab treatment, age at study enrollment, randomly assigned study treatment and BROCA-HR status. The estimated hazard ratio(s) for BROCA-HR and the corresponding confidence intervals will be depicted with a forest plot, and assessed for qualitative interaction(s) (Gail and Simon, 1985).

It is anticipated that 25-30% 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 HR deficiencies. Therefore, assuming that 20% of the deaths at the time of the final analysis have BROCA deficiencies, then the number of deaths among those patients with BROCA deficiencies in each pairwise treatment comparison is projected to (D1=0.20*(110+137)≈49. In this case, the variances of the log treatment hazard ratios are expected to be approximately 0.081 (4/D1 ≈ 4/49). Among those without BROCA-HR deficiencies the variances are expected to be about 0.020 (4/(0.80*(110+137)).

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 maker 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.

13.2.2.2 Circulating endothelial cells (CECs)

An increase in the level of 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 on the treatment (ie. 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 deviations 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 for each of the treatment groups selected for phase III evaluation assessed using descriptive statistics, 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 et.al, 1988) will be used to assess whether the 3-day CEC levels are independent of treatment. All of the patients who were randomly assigned to the reference regimen or one of the experimental regimens selected for phase III evaluation will be included in this analysis, regardless of whether they were enrolled during the phase II or the phase III component of this study, 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 that valid pre-treatment and 3-day measurements are available from 85% of the individuals in each treatment group (0.85*170=144) there is approximately 85% power to detect an effect size (difference in means/standard deviation) of 0.39. 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 death within each treatment group. 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 there is expected to be 110-137 deaths reported in each treatment group depending of each treatment's effect on overall survival. Assuming at least one experimental treatment is selected following the phase II component of the trial and 85% of individuals provide paired measurements, then this sample size (~250*0.85=212 deaths) provides 83% statistical power if the true reduction (or increase) in the hazard of death is 18% (HR=0.82) for individuals whose change in CEC values are one standard deviation apart (ie, one standard deviation of the change in CEC values). Patients who were enrolled onto the phase II study and randomized to treatments that were not selected for the phase III study may also be included in these analyses. A plot of the martingale residuals (Therneau et al, 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.

13.2.2.3 Plasma Angiome

This component of the study seeks to determine whether the angiogenic biomarkers in the plasma angiome are prognostic and/or predictive for survival. Pretreatment biologic specimens from individuals receiving chemotherapy or any of the experimental treatments will be quantified. Descriptive statistics and histograms will be used to assess the center and the dispersion of the values for each analyte, as well as identify outliers. Scattergrans and Spearman's rank correlation will be used to assess the associations between pairs of analytes.

A proportional hazards model (Cox, 1972) will be used to assess whether the pretreatment values of any of these analytes have a prognostic association with overall survival. The model will include clinical covariates: age, performance status, and the randomly assigned study treatment. A training set which includes a random selection of about 60% of the individuals in this study will be used to identify a subset of potentially prognostic analytes. Proportional hazards models will be used to assess the relationship between patients' analyte values and log hazard. At the time of the final analysis, there are expected to be 110 to 137 deaths in each treatment group selected for the phase III trial. Provided at least one experimental treatment group is selected following the phase II trial and 95% of the patients provide a pretreatment sample, this sample size (~250*0.95=237) provides 87% power if the true hazard of death is reduced (or increased) 18% (HR=0.82) for individuals who are separated by one standard deviation of the analyte. The results from these univariate analyses on individual analytes will be used to construct a multivariate classifier for prognosis. Once the classifier has been defined and documented, its validity will be independently evaluated among those individuals who were not included in the training set.

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

complete. 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 maintaining the documentation for 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. Though, the biospecimen identifiers will not be released so as not to compromise the validity of other validation studies that may use these samples for other purposes.

In a similar fashion, a proportional hazards model will be used to assess the potential predictive associations between analytes, treatment and survival. The models will include the covariates: age, performance status, randomly assigned study treatment, an analyte -by-treatment interaction term. In this case, focus will be on the analyte-by-treatment interaction terms. Those biomarkers that appear to be predictive will be used to construct a classifier for predicting responsiveness to treatment. Once this classifier has been defined and documented, its validity will be independently documented and evaluated using those individuals who were not included in the training set. The validation procedures will be similar to those described above.

Kaplan-Meier plots and forest plots will be used to summarize the associations between analytes and overall survival and relative risk of death.

13.3 Projected Race and Ethnicity of Enrollees (22-SEP-2022)

Anticipated Accrual by Race and Ethnicity

Assuming Full Phase 2 Accrual and Phase 3 Accrual to Three Treatment Arms

DOMESTIC

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	4	0	0	0	**4**
Asian	3	0	0	0	**3**
Native Hawaiian or other Pacific Islander	1	0	0	0	**1**
Black or African American	17	0	0	0	**17**
White	439	0	13	0	**452**
More than one race	0	0	0	0	**0**
Not Reported	0	0	0	0	**0**
TOTAL	**464**	**0**	**13**	**0**	**477**

FOREIGN

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	0	0	0	0	**0**
Asian	8	0	0	0	**8**
Native Hawaiian or other Pacific Islander	0	0	0	0	**0**
Black or African American	0	0	0	0	**0**
White	64	0	0	0	**64**
More than one race	0	0	0	0	**0**
Not Reported	0	0	0	0	**0**
TOTAL	**72**	**0**	**0**	**0**	**72**

14. EVALUATION CRITERIA

14.1 Antitumor Effect – Solid Tumors (06-AUG-2021)

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 disease progression, imaging studies should continue every 9 weeks (+/- 7 days) until progression. After 1 year of protocol therapy or follow-up (measured from approximately cycle 1, day 1), imaging studies will be conducted every 12 weeks. An Excel tool will be provided to sites to assist in determining imaging dates. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response; the next planned scan may be used as the confirmatory scan.

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.

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.

14.1.1 Definitions

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

Evaluable for objective 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.

14.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm 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 might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm 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.

14.1.3 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm 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.
The decisions are made on the diagnostic CT scans only if PET/diagnostic CT (with oral/iv contrast) is to be used for tumor measurements.
New lesions may 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.

14.1.4 Response Criteria

14.1.4.1 Evaluation of Target Lesions

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

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.

14.1.4.2 Evaluation of Non-Target Lesions

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

14.1.4.3 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 the date of randomization). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

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

* 'Non-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

14.1.5 Duration of Response

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

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

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

14.1.6 Progression-Free Survival

The onset of progression will be determined using RECIST criteria (Section 15.1.4). 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

The following PFS sensitivity analyses are planned. **(06-AUG-2021)**

1. Attrition-time bias: In addition to the PFS censoring rules described above, patients who receive non-protocol anticancer therapy before disease progression will be censored at the time of their last disease assessment before starting non-protocol therapy. The primary log-rank test 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.
2. Evaluation-time bias: An interval-censored log-rank test (as implemented in SAS® Proc ICLIFETEST) will be used.

15. REFERENCES

Abel HJ, et al. (2010) SLOPE: a quick and accurate method for locating non-SNP structural variation from targeted next-generation sequence data. Bioinformatics 26:2684-2688.

Adamo A, Collis SJ, Adelman CA, et al. Preventing nonhomologous end joining suppresses DNA repair defects of Fanconi anemia. Mol Cell 2010;39:25-35.

Baldwin RL, Nemeth E, Tran H, et al. BRCA1 promoter region hypermethylation in ovarian carcinoma: a population-based study. Cancer Res 2000;60:5329-33.

Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA et al. Reliability and validity of the functional assessment of cancer therapy-ovarian. J Clin Oncol. 2001; 19(6):1809-17.

Beesley VL, Green AC, Wyld DK et al. Quality of life and treatment response among women with platinum-resistant versus platinum-sensitive ovarian cancer treated for progression: a prospective analysis. Gyn Onc 2014; 132(1): 130-06.

Berk KN and Lachenbruch PA. Repeated measures with zeros. Stat Methods in Med Res 2003, 11(4): 303-316.

Birkbak NJ, Wang ZC, Kim JY, et al. Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents. Cancer Discov 2012;2:366-75.

Bouwman P, Aly A, Escandell JM, et al. 53BP1 loss rescues BRCA1 deficiency and is associated with triple-negative and BRCA-mutated breast cancers. Nature structural & molecular biology 2010;17:688-95.

Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005;434:913-7.

Bunting SF, Callen E, Wong N, et al. 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. Cell 2010;141:243-54.

Cannistra SA. Cancer of the ovary. The New England journal of medicine 2004;351:2519-29.

Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. Journal of Allergy and Clinical Immunology 2008; 122(3): 574-580

Cella D, Neubauer N, Thomas J et al. The FACIT-AI, a new tool for assessing symptoms associated with malignant ascites. Gynecol Oncol. 2013; 128(2):187-90.

Cox, DR. Regression Models and life tables (with discussion), J of the Royal Statistical Society B 1972, 26: 103-110.

Du Bois A, Luck HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003;95:1320-9.

Duric VM, Stockler MR, Heritier S et al. Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes AC and CMF worthwhile now? Ann Oncol. 2005; 16 (11):1786-94. Epub 2005 Aug 26.

Esteller M, Silva JM, Dominguez G, et al. Promoter hypermethylation and BRCA1 inactivation in sporadic breast and ovarian tumors. J Natl Cancer Inst 2000;92:564-9.

Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917-21.

Freidlin, B, Korn, EL and George, SL, Data monitoring committees and interim monitoring guidelines, Controlled Clinical Trials 1999; 20:395-407.

Friedlander ML, Stockler M, O'Connell R et al. Symptom burden and outcomes of patients with platinum resistant/refractory recurrent ovarian cancer: a reality check: results of stage 1 of the gynecologic cancer intergroup symptom benefit study. Int J Gynecol Cancer. et al, IJGC 2014; 24(5):857-64.

Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123-34.

Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28:2512-9.

Gail M and Simon R. Testing for qualitative interactions between treatment effects and patient subsets. Biometrics 1983, 41(2): 361-372.

Garg K, Levine DA, Olvera N et al. BRCA1 immunohistochemistry in a molecularly characterized cohort of ovarian high-grade serous carcinomas. Am J Surg Pathol. 2013;37(1):138-46.

Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. The lancet oncology 2011;12:852-61.

Goon PKY, Lip GYH, Boos CJ et al., Circulating Endothelial Cells, Endothelial Progenitor Cells, and Endothelial Microparticles in Cancer. Neoplasia. 2006; 8(2): 79–88.

Jensen SE, Rosenbloom SK, Beaumont JL et al. A new index of priority symptoms in advanced ovarian cancer. Gynecol Oncol. 2011; 120(2):214-9.

Johnson N, Johnson SF, Yao W, et al. Stabilization of mutant BRCA1 protein confers PARP inhibitor and platinum resistance. Proceedings of the National Academy of Sciences of the United States of America 2013;110:17041-6.

Kaplan EL and Meier P. Nonparametric estimation from incomplete observations. J of the American Statistical Assoc 1958, 53: 457-481.

Kaye SB, Lubinski J, Matulonis U, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol 2012;30:372-9.

Kleinbaum DG, Kupper LL and Muller KE (1988). Applied Regression Analysis and other Multivariate Methods, 2nd edition, Duxberry Press, Belmont, CA.

Kummar S, Gutierrez ME, Chen A, et al. Phase I trial of vandetanib and bevacizumab evaluating the VEGF and EGF signal transduction pathways in adults with solid tumours and lymphomas. Eur J Cancer 2011;47:997-1005.

Lan GKKK, Demets, DL, Group Sequential Procedures: Calendar vs Information Time, Stats in Med 1989; 8:1191-8.

Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014;15(8):852-61.

Ledermann JA PJ, Raja FA, et al. Randomised double-blind phase III trial of cediranib (AZD 2171) in relaposed platinum sensitive ovarian cancer: Results of the ICON6 trial. Presented at the 38th Congress of the European Society for Medical Oncology (ESMO) 2013, Abst LBA10.

Ledermann JA, Kristeleit RS. Optimal treatment for relapsing ovarian cancer. Ann Oncol 2010;21 Suppl 7:vii218-22.

Lee JM, Hays JL, Annunziata CM, et al. Phase I/Ib Study of Olaparib and Carboplatin in BRCA1 or BRCA2 Mutation-Associated Breast or Ovarian Cancer With Biomarker Analyses. Journal of the National Cancer Institute 2014;106.

Lee JM, Ledermann JA, Kohn EC. PARP Inhibitors for BRCA1/2 mutation-associated and BRCA-like malignancies. Ann Oncol 2014;25:32-40.

Lee JM, Trepel JB, Choyke P, et al. CECs and IL-8 have prognostic and predictive utility in patients with recurrent platinum-sensitive ovarian cancer: biomarker correlates from the

randomised phase 2 trial of olaparib and cediranib verses olaparib in recurrent platinum-sensitive ovarian cancer. Front Oncol 2015, in press.

Lin Y, Weisdorf DJ, Solovey A et al,. Origins of circulating endothelial cells and endothelial outgrowth from blood. J Clin Invest. 2000;105(1):71–77.

Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol. 2014 Oct;15(11):1207-14.

Liu JF, Tolaney SM, Birrer M, et al. A Phase 1 trial of the poly(ADP-ribose) polymerase inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer. Eur J Cancer 2013;49:2972-8.

Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet 2011;advance online publication.

Markman M, Bookman MA. Second-line treatment of ovarian cancer. Oncologist 2000;5:26-35.

Markman M, Kennedy A, Webster K et al., Paclitaxel-Associated Hypersensitivity Reactions: Experience of the Gynecologic Oncology Program of the Cleveland Clinic Cancer Center. J Clin Oncol 2000;18:102-105

Matsuo K, Lin YG, Roman LD, Sood AK. Overcoming platinum resistance in ovarian carcinoma. Expert Opin Investig Drugs 2010;19:1339-54.

Matulonis UA, Berlin S, Ivy P, et al. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. J Clin Oncol 2009;27:5601-6.

McCabe N, Turner NC, Lord CJ, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res 2006;66:8109-15.

McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. The New England journal of medicine 1996;334:1-6.

Meindl A, Hellebrand H, Wiek C, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet 2010;42:410-4.

Network TCGA. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-15.

Nik-Zainal S, Alexandrov LB, Wedge DC, et al. Mutational processes molding the genomes of 21 breast cancers. Cell 2012;149:979-93.

Ning YM, Gulley JL, Arlen PM, et al. Phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2010;28:2070-6.

Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003;21:3194-200.

Park SR, Speranza G, Piekarz R, et al. A multi-histology trial of fostamatinib in patients with advanced colorectal, non-small cell lung, head and neck, thyroid, and renal cell carcinomas, and pheochromocytomas. Cancer Chemother Pharmacol 2013;71:981-90.

Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 2003;361:2099-106.

Patel AG, Sarkaria JN, Kaufmann SH. Nonhomologous end joining drives poly(ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells. Proc Natl Acad Sci U S A 2011;108:3406-11.

Pennington KP, et al. (2012) BRCA1, TP53, and CHEK2 germline mutations in uterine serous carcinoma. Cancer.

Pennington KP, Walsh T, Harrell MI et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res. 2014;20(3):764-75.

Pennington KP, Walsh T, Harrell MI, et al. Germline and Somatic Mutations in Homologous Recombination Genes Predict Platinum Response and Survival in Ovarian, Fallopian Tube, and Peritoneal Carcinomas. Clinical cancer research : an official journal of the American Association for Cancer Research 2013.

Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15.

Rafii S, Lyden D, Benezra R et al. Vascular and haematopoietic stem cells: novel targets for anti-angiogenesis therapy? Nature Reviews Cancer 2002; 2:826-835.

Rafnar T, Gudbjartsson DF, Sulem P, et al. Mutations in BRIP1 confer high risk of ovarian cancer. Nat Genet 2011.

Ramsey S, Willke R, Briggs A et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Health. 2005; 8(5):521-33. Review.

Stockler MR, Hilpert F, Friedland M et al, Patient-Reported Outcome Results From the Open-Label Phase III AURELIA Trial Evaluating Bevacizumab- Containing Therapy for Platinum-Resistant Ovarian Cancer. J Clin Onc 2013; 32(13):1309-16

Swisher EM, Gonzalez RM, Taniguchi T, et al. Methylation and protein expression of DNA repair genes: association with chemotherapy exposure and survival in sporadic ovarian and peritoneal carcinomas. Molecular cancer 2009;8:48.

Thrall M, Gallion HH, Kryscio R, et al. BRCA1 expression in a large series of sporadic ovarian carcinomas: a Gynecologic Oncology Group study. Int J Gynecol Cancer 2006;16 Suppl 1:166-71.

Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proceedings of the National Academy of Sciences of the United States of America 2011;108:18032-7.

Walsh T, Lee MK, Casadei S, et al. Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. Proceedings of the National Academy of Sciences of the United States of America 2010;107:12629-33.

Wang ZC, Birkbak NJ, Culhane AC, et al. Profiles of genomic instability in high-grade serous ovarian cancer predict treatment outcome. Clin Cancer Res 2012;18:5806-15.

Wickramanyake A, Bernier G, Pennil C, et al. Loss of function germline mutations in RAD51D in women with ovarian carcinoma. Gynecologic oncology 2012.

Wiggans AJ1, Cass GK, Bryant A et al. Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. Cochrane Database Syst Rev. 2015 May 20;5: CD007929. [Epub ahead of print]

APPENDIX I. COLLABORATIVE AGREEMENT

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, and other relevant Health Authorities 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 II. PERFORMANCE SCALE

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

APPENDIX III. PATIENT DRUG DIARY

CEDIRANIB ONLY (12/05/2016)

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

1. Complete one form for each cycle (28 days).
3. Record the date, the number of pills you took, and when you took them.
4. Bring your pill bottles (including empty bottles) and this form to every appointment.
5. Do not chew, dissolve, or crush medications. DO NOT make up vomited doses.
6. 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.
7. The first row in the table below is an EXAMPLE ROW for how to complete this diary.

CEDIRANIB
Take __(number) ____mg and __(number) ____ mg tablets once daily. Take on an empty stomach.

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

Patient's Signature: _____ Date: _____

Physician/Nurse's Signature _____ Date_____

OLAPARIB ONLY (12/05/2016)

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*
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Patient's Signature: _____ Date: _____

Physician/Nurse's Signature _____ Date _____

CEDIRANIB AND OLAPARIB (12/05/2016)

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

7. Complete one form for each cycle (28 days).
8. Record the date, the number of tablets you took, and when you took them.
9. Bring your pill bottles (including empty bottles) and this form to every appointment.
10. Do not chew, dissolve, or crush medications. DO NOT make up vomited doses.
11. 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.
12. 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.**

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

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*
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Patient's Signature: _____ Date: _____
Physician/Nurse's Signature _____ Date_____

APPENDIX IV: 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's Signature _____ Date _____

APPENDIX V: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD (12/05/2016)

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." AZD2171 (cediranib) 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 _____.

PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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 UGT1A1enzymes 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

STUDY DRUG INFORMATION WALLET CARD

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:

- 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.

- 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 _____.

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.

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

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

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

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

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		

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

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

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

APPENDIX VI: ORAL ANTIHYPERTENSIVE MEDICATIONS.

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	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate

β Blockers (BB)	**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
Dihydro-pyridine 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 VII – TRANSLATIONAL SCIENCE SPECIMEN PROCEDURES

Sites in Korea: Please refer to Appendix XIV for biospecimen requirements and procedures. Information in this appendix is not applicable to sites in Korea.

I. Obtaining a Bank ID for Translational Science Specimens (12/05/2016)

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@nrgoncology.org; Phone: 716-845-7767).

II. CEC Whole Blood
Shipped to the Preclinical Development Research Core

Note: Sites in Japan and Korea should not collect CEC whole blood specimens.

A. Requesting CEC Whole Blood Specimen Kits (12/05/2016)

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). Sites must provide their own shipping kits and cover shipping costs.**

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 (12/05/2016)
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
Shipped to the NRG Oncology Biospecimen Bank-Columbus (NRG BB-Columbus)

A. Requesting Translational Science Specimen Kits (12/05/2016)
Specimen kits are not provided for the collection and shipment of **BROCA-HR whole blood and FFPE specimens** shipped to the NRG BB-Columbus.

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** should not be ordered

until the time of disease progression or end of treatment. One of the Research Plasma kits should be used to ship the Future Use Whole Blood (WB04), in addition to the Research Plasma.

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. The NRG BB-Columbus will not provide additional CPT (citrate) tubes if the site fails to use them by the expiration date.

Sites can order kits online via the Kit Management link (**https://kits.bpc-apps.nchri.org/**). **(27-AUG-2021).** 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. A pre-paid shipping label for the return of unused supplies and kits may be obtained via the Kit Management system. Select "Empty Kit" for package contents when returning unused kits.

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
Note: Sites in Korea should not collect CEC whole blood specimens.

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 (FP01/FM01; section 11.2.1.2) and a **block will be submitted on a permanent basis to fulfill both the mandatory (FP02/FM02; section 11.2.1.1) and optional (FP01/FM01; section 11.2.1.2) specimen requirements, then label the **block** FP01 (for primary) or FM01 (for metastatic). Complete and ship both the FP01 and FP02 (for primary) or FM01 and FM02 (for metastatic) 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). **Primary** and **metastatic** tumor should be collected prior to all treatment. **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**. Only one block may be submitted per tissue type.

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.*

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.

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 -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

F. 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 4ºC (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 4ºC (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 -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

G. Shipping Translational Science Specimens (12/05/2016)
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-GY005
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://kits.bpc-apps.nchri.org/). **(27-AUG-2021**). 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 ≤-70ºC 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 link (https://kits.bpc-apps.nchri.org/). **(27-AUG-2021).** 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 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).

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 <u>further</u> 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 VIII – TRANSLATIONAL SCIENCE LABORATORY TESTING PROCEDURES

I. BROCA-HR

A. Overview

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 formnalin-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 pipleline (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 senstivity 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 willd type background.

C. References

1. Nord AS, et al.(2011) Accurate and exact CNV identification from targeted high-throughput sequence data. BMC Genomics 12:184.
2. Walsh T, et al. (2011) Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci.
3. Walsh T, et al. (2010) Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. Proc Natl Acad Sci 107:12629-12633.
4. Pritchard CC, et al. (2012) ColoSeq Provides Comprehensive Lynch and Polyposis Syndrome Mutational Analysis Using Massively Parallel Sequencing. J Mol Diagn 14:357-366.
5. Pennington KP, et al. (2012) BRCA1, TP53, and CHEK2 germline mutations in uterine serous carcinoma. Cancer.
6. Abel HJ, et al. (2010) SLOPE: a quick and accurate method for locating non-SNP structural variation from targeted next-generation sequence data. Bioinformatics 26:2684-2688.
7. Osorio A, et al. (2012) Predominance of pathogenic missense variants in the RAD51C gene occurring in breast and ovarian cancer families. Hum Mol Genet 21:2889-2898.
8. Bouwman P, et al. (2013) A high-throughput functional complementation assay for classification of BRCA1 missense variants. Cancer Discov.

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 -80ºC and then 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 x 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 labaoratory 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 (Ning et al. 2010, Park et al. 2013 and Thomas et al. 2015).
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., 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 ($p<0.05$). (Lee et al. manuscript submitted) 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 siginificant differences 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 ($p <0.001$; Jacques et al. J Immunol Methods 2008). 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 +/− SD, 25.6 +/− 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 (Jacques et al. J Immunol Methods 2008; Park et al. Cancer Chemother Pharmacol 2013). 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. Eight 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 1000µL pipette and transfer to a labeled cryotube. Collect PBMC layer (approximately between 1-3mL) with a 1000µL 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 10µL 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 -80ºC 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

1. Lee JM, et al (2015) Development of a multiparameter flow cytometric assay as a potential biomarker for homologous recombination deficiency in women with high-grade serous ovarian cancer (submitted)
2. Jacques N, et al. (2008) Quantification of circulating mature endothelial cells using a whole blood four-color flow cytometric assay. J Immunol Methods
3. Park SR, et al. (2013) A multi-histology trial of fostamatinib in patients with advanced colorectal, non-small cell lung, head and neck, thyroid, and renal cell carcinomas, and pheochromocytomas. Cancer Chemother Pharmacol
4. Ning YM, Gulley JL, Arlen PM, et al. Phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2010;28:2070-6.
5. Park SR, Speranza G, Piekarz R, et al. A multi-histology trial of fostamatinib in patients with advanced colorectal, non-small cell lung, head and neck, thyroid, and renal cell carcinomas, and pheochromocytomas. Cancer Chemother Pharmacol 2013;71:981-90.
6. Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. Lancet Oncol. 2015;16(2):177-86.
7. Jacques N, Vimond N, Conforti R et al. Quantification of circulating mature endothelial cells using a whole blood four-color flow cytometric assay. J Immunol Methods 2008 ;337(2):132-43

III. Olaparib and Cederanib 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 anonymised by pooling. Additional analyses may be conducted on the anonymised, 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. Anonymised samples will be retained for no more than 5 years after the Clinical Study Report is finalised.

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.

IV. 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

1. Liu Y, Starr MD, Bulusu A, Pang H, Wong NS, Honeycutt W, Amara A, Hurwitz HI, **Nixon AB**. (2013) Correlation of angiogenic biomarker signatures with clinical outcomes in metastatic colorectal cancer patients receiving capecitabine, oxaliplatin, and bevacizumab. Cancer Med. 2(2):234-242.
2. **Nixon AB**, Pang H, Starr MD, Friedman PN, Bertagnolli MM, Kindler HL, Goldberg RM, Venook AP, Hurwitz HI. (2013) Prognostic and predictive blood-based biomarkers in patients with advanced pancreatic cancer: Results from CALGB 80303 (Alliance). Clin Cancer Res. 19(24):6957-66.

3. **A.B. Nixon**, S. Halabi I. Shterev, M.D. Starr, J.C Brady, J. Dutcher, J. Hopkins, H.I. Hurwitz, E. Small, B. Rini, P.G. Febbo, D. George (2013) Identification of predictive biomarkers of overall survival (OS) in patients (pts) with advanced renal cell carcinoma (RCC) treated with interferon alpha (I) +/- bevacizumab (B): Results from CALGB 90206 (Alliance) J Clin Oncol. 2013;31:Suppl; abstr 4520.
4. A.J. Hatch, H. Pang, M.D. Starr, J.C. Brady, J. Jia, D. Niedzwiecki, A.P. Venook, S.M. Cushman, H.I. Hurwitz, **A.B. Nixon**. (2014) Prognostic and predictive blood-based biomarkers of overall survival (OS) in patients (pts) with advanced colorectal cancer (CRC) treated with cetuximab (C): Results from CALGB 80203 (Alliance). J Clin Oncol 32:5s, 2014 (suppl; abstr 11022).
5. Liu Y, Starr MD, Brady JC, Dellinger A, Pang H, Adams B, Theuer CP, Lee NY, Hurwitz HI, **Nixon AB**. (2014) Modulation of circulating protein biomarkers following TRC105 (anti-endoglin antibody) treatment in patients with advanced cancer. Cancer Med. Jun; 3(3): 580-91.

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: methylation % = [peak height methylated/(peak height methylated + 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 routine 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 ($R2 > 0.99$) 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 (5µm 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: methylation % = [peak height methylated / (peak height methylated + 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

1. Banerjee S, Kaye SB, Ashworth A: Making the best of PARP inhibitors in ovarian cancer. Nat Rev Clin Oncol 7:508-19, 2010
2. Colella S, Shen L, Baggerly KA, et al: Sensitive and quantitative universal Pyrosequencing methylation analysis of CpG sites. Biotechniques 35:146-50, 2003
3. Tost J, Dunker J, Gut IG: Analysis and quantification of multiple methylation variable positions in CpG islands by Pyrosequencing. Biotechniques 35:152-6, 2003
4. Ronaghi M, Uhlen M, Nyren P: A sequencing method based on real-time pyrophosphate. Science 281:363, 365, 1998
5. Dejeux E, Audard V, Cavard C, et al: Rapid identification of promoter hypermethylation in hepatocellular carcinoma by pyrosequencing of etiologically homogeneous sample pools. J Mol Diagn 9:510-20, 2007

6. Garg K, Levine DA, Olvera N, et al: BRCA1 immunohistochemistry in a molecularly characterized cohort of ovarian high-grade serous carcinomas. Am J Surg Pathol 37:138-46, 2013

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; 3,30-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 will be performed. The stains will be 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 will be used to develop categorical criteria for scoring cases as BRCA1 loss, BRCA1 retained, or BRCA1 equivocal. Two independent and blinded pathologists will validate these criteria. In our published work (Garg et al., 2013) we demonstrated that this assay has a PPV of 94%, NPV of 92%, sensitivity of 86% and specificity of 97%.

C. References

1. Meisel JL, Hyman DM, Garg K, Zhou Q, Dao F, Bisogna M, Gao J, Schultz ND, Grisham RN, Phillips M, Iasonos A, Kauff ND, Levine DA, Soslow RA, Spriggs DR. The performance of BRCA1 immunohistochemistry for detecting germline, somatic, and epigenetic BRCA1 loss in high-grade serous ovarian cancer. Ann Oncol. 2014 Dec;25(12):2372-8. doi: 10.1093/annonc/mdu461. Epub 2014 Oct 3. PubMed PMID: 25281711; PubMed Central PMCID: PMC4271017.
2. Reyes MC, Arnold AG, Kauff ND, Levine DA, Soslow RA. Invasion patterns of metastatic high-grade serous carcinoma of ovary or fallopian tube associated with BRCA deficiency.

Mod Pathol. 2014 Oct;27(10):1405-11. doi: 10.1038/modpathol.2013.237. Epub 2014 Feb 28. PubMed PMID: 24577588.

3. Garg K, Levine DA, Olvera N, Dao F, Bisogna M, Secord AA, Berchuck A, Cerami E, Schultz N, Soslow RA. BRCA1 immunohistochemistry in a molecularly characterized cohort of ovarian high-grade serous carcinomas. Am J Surg Pathol. 2013 Jan;37(1):138-46. doi: 10.1097/PAS.0b013e31826cabbd. PubMed PMID: 23232854; PubMed Central PMCID: PMC3531916.
4. Soslow RA, Han G, Park KJ, Garg K, Olvera N, Spriggs DR, Kauff ND, Levine DA. Morphologic patterns associated with BRCA1 and BRCA2 genotype in ovarian carcinoma. Mod Pathol. 2012 Apr;25(4):625-36. doi: 10.1038/modpathol.2011.183. Epub 2011 Dec 23. PubMed PMID: 22193042.

Appendix IX: 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 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) as well as 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 mean scores 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.

Cost-effectiveness:

Cost-effectiveness (cost utility) will be evaluated using a health-related quality of life (HRQoL) metric (utility) derived from the 5-item EQ5D. OS may additionally inform cost-effectiveness in the Phase III study.
Using the EQ-5D, we will:
1. Compare treatment arms to each other at all study time points.

2. Compare pre-progression to post-progression.

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 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
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
DRS-P	GP4	I have pain	0	1	2	3	4
DRS-P	GP6	I feel ill	0	1	2	3	4
DRS-P	O3	I have cramps in my stomach area	0	1	2	3	4
DRS-P	HI7	I feel fatigued	0	1	2	3	4
DRS-P	Cx6	I am bothered by constipation	0	1	2	3	4
DRS-P	O1	I have swelling in my stomach area	0	1	2	3	4
DRS-P	C3	I have control of my bowels	0	1	2	3	4
DRS-P	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
DRS-E	GP2	I have nausea	0	1	2	3	4
TSE	B5	I am bothered by hair loss	0	1	2	3	4
TSE	GP5	I am bothered by side effects of treatment	0	1	2	3	4
TSE	O2	I have been vomiting	0	1	2	3	4
TSE	BMT15	I am bothered by skin problems	0	1	2	3	4
FWB	BMT5	I am able to get around by myself	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4
FWB	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)

03 March 2010
Page 1 of 1

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 <u>past 7 days</u>.**

		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 X: Plan for QOL compliance

NRG will utilize the following strategies to optimize QOL long-term compliance:

TARGET: CLINICAL RESEARCH ASSOCIATES & NURSING
Task 1. **Presentation** at each semi-annual group meeting on compliance updates and challenges, sharing QOL results, and reinforcing the message that QOL should continue to be assessed after the patient progresses or is off the study treatment.
Assigned to: Presenters will include the leadership of the data management and nursing committees.
Task 2. Send an initial **email message, prior to study activation** to all institutions' CRA's, nurses and site PI detailing the requirements, and procedures for QOL data collection, along with the importance of continuing timely assessments.
Assigned to: This message can be prepared by the QOL study chair together with the Data Management and Nursing committee leaders.
Task 3. **Quarterly distribution list email message** to the data management and nursing committees on compliance updates and challenges, reinforcing the message that QOL should continue to be assessed after the patient progresses or is off the study treatment.
Assigned to: Compliance reports will be prepared by the statistical office, and the email message will be sent by the PCOR leaders.
Task 4. **Newsletters** with study updates, including QOL compliance can be prepared semi-annually for activated trials. Sites that are doing especially well with compliance can be featured.
Assigned to: The QOL study Chair, the study statistician and the data management leaders should contribute to individual study updates.
Task 5. The IT staff is developing a **forms-due calendar** in Medidata/Rave to remind clinic staff of upcoming assessments for each patient.Assigned to: IT Staff with oversight from the Statistical Office
Task 6. A patient **form schedule** is provided to the institution at the time of registration, indicating due dates for QOL assessments.
Assigned to: IT Staff with oversight from the Statistical Office
Task 7. A monthly **forms tracking list** is provided to the institutions, listing all forms due, including QOL, projecting 30 days in advance.
Assigned to: IT Staff with oversight from the Statistical Office
Task 8. A **14-day advance notice** is sent to institutions notifying them of QOL assessments that will be due. **Past due notifications** will be sent out 15, 30, 60 and 90 days to the data management CRAs with site PIs copied.
Assigned to: IT Staff with oversight from the Statistical Office
Task 9. **Delinquency reports** will be generated with expectation of 80% compliance, sent to site PIs and CRAs.
Assigned to: IT Staff with oversight from the Statistical Office

TARGET: PATIENT ADVOCATES
Task 1. Provide advice on **strategies to improve awareness** of the importance of timely and complete QOL data (e.g., brochure, letter, message in the informed consent).
Assigned to: Disease site patient advocates.

Appendix XI: Protocol Monitoring Plan (12/05/2016) (06-AUG-2021)

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 from the centralized monitoring. The source records for the eligilibity 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 Study Chair. Findings associated with centralized monitoring also should be reported to CTMB (frequency and mechanism for reporting to be discussed as part of the Monitoring Working Group that is being established).

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, 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 timepoints: (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 discharges.
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 every enrolled patient from just before initiating study treatment up until progression or death, whichever occurs first, will be prospectively collected and stored electronically. All collected images will be appropriately de-identified. If it is deemed appropriate, these images will be available for trained independent radiologists to review in a standardized fashion. Also, if 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 RCRHelpDesk@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 XII: NRG General Guidelines (12/05/2016)

- 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 XIII: DIAGNOSTIC IMAGE COLLECTION SUMMARY (12/05/2016)

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.

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 XIV – KGOG BIOSPECIMEN REQUIREMENTS

I. Integrated Biomarker Biospecimen Requirements

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.

Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens To
BROCA-HR FFPE – Submit *one* of the following		
BROCA-HR FFPE Primary Tumor (FP02)[2] 2 unstained slides (charged, 10µm)[2]	Prior to all treatment *Submit one tissue type (FP02 or FM02) with FP02 being the preferred tissue type.*	KGOG central lab within 8 weeks of registration[3]
BROCA-HR FFPE Metastatic Tumor (FM02)[1] 2 unstained slides (charged, 10µm)[2]		
BLOOD		
Future Use Whole Blood (WB04) 7-10mL drawn into purple top (EDTA) tube(s) and frozen[4]	Prior to GY005 study treatment	KGOG central lab within 5 weeks of registration[3]

1 An English translated copy of the corresponding pathology report **must** be shipped with all tissue specimens sent to the NRG BB-Columbus. Note: The entire report must be translated, typed, and include diagnosis, clinical history, gross description or block number, and microscopic findings.
2 Please refer to additional details in section V, A, c: "Special Instructions for BROCA-HR and Optional FFPE Submission"
3 Sites should ship to the KGOG central lab. The KGOG central lab will batch ship all biospecimens to the US.
4 Do not use glass blood collection tubes.

II. Exploratory Biomarker Specimen Requirements

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.

Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens To
FFPE – Submit *one* of the following		
FFPE Primary Tumor (FP01)[1] 1st Choice: block[2] 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to all treatment *Submit one tissue type (FP02 or FM02) with FP02 being the preferred tissue type.*	KGOG central lab within 8 weeks of registration[3]
FFPE Metastatic Tumor (FM01)[1] 1st Choice: block[2] 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)		
FFPE Recurrent Primary Tumor (FRP01)[1] 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment, only if FFPE tumor collected prior to all treatment is not available (i.e., FP01 or FM01) *Submit one tissue type (FRP01 or FRM01) with FRP01 being the preferred tissue type.*	
FFPE Recurrent Metastatic Tumor (FRM01)[1] 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)		
BLOOD		
Research Pre-treatment Plasma (PB09) prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)	Prior to GY005 study treatment	KGOG central lab within 5 weeks of registration[4]

Research C2D1 Plasma (PB10) prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)	Cycle 2, day 1, prior to GY005 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 GY005 treatment, only if PB09 was submitted	KGOG central lab within 26 weeks of registration[4]

1 An English translated copy of the corresponding pathology report **must** be shipped with all tissue specimens sent to the NRG BB-Columbus. Note: The entire report must be translated, typed, and include diagnosis, clinical history, gross description or block number, surgical pathology ID number and microscopic findings.
2 Please refer to additional details in section V, A, c: "Special Instructions for BROCA-HR and Optional FFPE Submission"
3 Sites should ship to the KGOG central lab. The KGOG central lab will batch ship all biospecimens to the US.

III. Obtaining a Bank ID for Translational Science Specimens

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@nrgoncology.org).

IV. Requesting Translational Science Specimen Kits

Translational science biospecimen kits are not provided by the NRG BB-Columbus for sites in Korea.

V. FFPE

A. Instructions for Sites in Korea

a. BROCA-HR FFPE: Patients must agree to submit this mandatory specimen.
Only **one** tumor type should be submitted. The tissue submitted should be the most representative of the biospecimen type (e.g., primary tumor, metastatic tumor).

- BROCA-HR **primary** (FP02) or **metastatic** (FM02) tumor should be collected prior to all treatment.

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then two consecutive unstained slides cut sequentially from one block must be provided. Each tissue section **must** be cut at 10 microns and placed on positively charged slides.

b. OPTIONAL FFPE
Only **one** tumor type should be submitted. The tissue submitted should be the most representative of the biospecimen type (e.g., primary tumor, metastatic tumor, recurrent tumor).

- **Primary** or **metastatic** tumor should be collected prior to all treatment.

- **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 20 unstained slides cut sequentially from one block must be provided:

- **Ten** of these slides must be cut at **five microns** and placed on **positively charged slides**.
- **Ten** of these slides must be cut at **ten microns** and placed on **uncharged slides.**

c. Special Instructions for BROCA-HR and Optional FFPE Submission

- **Patient does not consent to optional FFPE collection**: Submit the two mandatory unstained sections for BROCA-HR (FP02 *or* FM02) only. Complete the corresponding specimen transmittal form (Form TR).
- **Patent consents to optional FFPE collection and slides will be submitted**: Submit the two mandatory unstained sections for BROCA-HR (FP02 *or* FM02) and 20 unstained sections for the optional FFPE collection (FP01, FM01). Complete the corresponding specimen transmittal forms (Form TR) for *both* slide sets.
- **Patient consents to optional FFPE collection and slides will be submitted for BROCA-HR, but a block will be submitted for optional FFPE collection:** Submit the two mandatory unstained sections for BROCA-HR (FP02 *or* FM02). Submit a block for the optional FFPE collection (FP01, FM01). Complete the corresponding specimen transmittal forms (Form TR) for *both* the slides and the block.
- **Patient consents to optional FFPE collection and a block will be submitted for both BROCA-HR and the optional FFPE collection:** Submit block labeled as FP01 or FM01 and complete the corresponding specimen transmittal form (Form TR). The FP02 and FM02 specimen transmittal forms (Form TR) should be completed as not collected; specify "submitted for other study."

d. Labeling Translational Science Specimens

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

Bank ID (# # # # - # # - G # # #)
protocol number (NRG-GY005)
specimen code (see sections I and II, as well as "special instructions" below)
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.

e. 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.

f. Pathology Reports
An English translated copy of the corresponding pathology report **must** be shipped with all tissue specimens sent to the NRG BB-Columbus. Note: The entire report must be translated, typed, and include diagnosis, clinical history, gross description or block number, surgical pathology ID number, and microscopic findings.

g. Shipping FFPE
Sites in Korea should ship FFPE to the KGOG Central Lab within eight weeks of patient registration.

B. Instructions for the KGOG Central Lab
FFPE blocks and unstained sections should be batched shipped to the NRG Oncology Biospecimen Bank-Columbus (Columbus, Ohio, USA) every 4-5 weeks. A completed copy of Form TR and the corresponding translated pathology report **must** be included for each patient and time point. The KGOG Central Lab should contact the NRG Oncology Biospecimen Bank-Columbus by email (bpcbank@nationwidechildrens.org) prior to shipping to confirm that the shipping date is appropriate. Specimen packaging must comply with IATA standards (www.iata.org).

C. Instructions for the NRG BB-Columbus
The NRG BB-Columbus will batch ship FFPE to Dr. Elizabeth Swisher (University of Washington, Seattle, WA, USA) every six months for BROCA-HR testing. Specimens from Korea will be included in regularly scheduled shipments.

VI. Future Use Whole Blood (WB04)

A. Instructions for Sites in Korea

a. Processing 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 -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC

freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

b. Labeling Future Use Whole Blood

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

Bank ID (# # # # - # # - G # # #)
protocol number (NRG-GY005)
specimen code (WB04)
collection date (mm/dd/yyyy)

c. Shipping Whole Blood

Sites in Korea should ship whole blood to the KGOG Central Lab within five weeks of patient registration.

B. Instructions for the KGOG Central Lab

Frozen whole blood should be batched shipped to the NRG Oncology Biospecimen Bank-Columbus (Columbus, Ohio, USA) every 4-5 weeks. A completed copy of Form TR **must** be included for each patient and time point. The KGOG Central Lab should contact the NRG Oncology Biospecimen Bank-Columbus by email (bpcbank@nationwidechildrens.org) prior to shipping to confirm that the shipping date is appropriate. Specimen packaging must comply with IATA standards (www.iata.org). Frozen biospecimens should be shipped by an international courier (e.g., World Courier) that will replenish dry ice in transit.

C. Instructions for the NRG BB-Columbus

The NRG BB-Columbus will bank frozen whole blood until requested by the sponsor for suture olaparib assay development.

VII. Research Plasma (PB09-PB11)

A. Instructions for Sites in Korea

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.

a. Processing Research Plasma

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 4ºC (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 4ºC (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 -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC 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.*

b. Labeling Research Plasma
A waterproof permanent marker or printed label should be used to label each translational science Research plasma specimen with:

Bank ID (# # # # - # # - G # # #)
protocol number (NRG-GY005)
specimen code (see section I)
collection date (mm/dd/yyyy)

c. Shipping Plasma
Sites in Korea should ship plasma to the KGOG Central Lab within five weeks of patient registration.

B. Instructions for the KGOG Central Lab
Frozen research plasma should be batched shipped to the NRG Oncology Biospecimen Bank-Columbus (Columbus, Ohio, USA) every 4-5 weeks. A completed copy of Form TR **must** be included for each patient and time point. The KGOG Central Lab should contact the NRG Oncology Biospecimen Bank-Columbus by email (bpcbank@nationwidechildrens.org) prior to shipping to confirm that the shipping date is acceptable. Specimen packaging must comply with IATA standards (www.iata.org). Frozen biospecimens should be shipped using an international courier (e.g., World Courier) that will replenish dry ice in transit.

C. Instructions for the NRG BB-Columbus
The NRG BB-Columbus will batch ship frozen research plasma to Dr. Andrew Nixon (Duke University, Chapel Hill, North Carolina, USA) for testing following all appropriate NCTN approval.

VIII. Submitting Form TR

A specimen transmittal form (i.e., Form TR) for each biospecimen will be available in the **Translational Research Folder in Rave**, once the Specimen Consent (located in the Baseline Folder) has been completed.

An electronically (i.e., Rave) completed copy of Form TR must accompany each biospecimen shipped to the NRG BB-Columbus. Handwritten forms will not be accepted.

Note: A copy does not need to be sent to the NRG BB-Columbus if biospecimens are not submitted.

Form TR **must** 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 not use the "Printable Version" or "View PDF" links at the bottom of the form or any other method to print the form, 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@nrgoncology.org; Phone: +17168457767).

IX. 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 XV – KGOG GUIDELINES FOR PLATELET COUNT DECREASED

To be consistent with the national approval of Olaparib (AZD2281) by the Ministry of Food and Drug Safety (MFDS) of Korea, 'platelet count decreased' will be kept as 'Less Likely (<=20%)' in the adverse events with possible relationship to Olaparib (Section 7.3.2) for the sites in Korea. This exemption related to 'platelet count decreased' will continue to apply throughout the study, regardless of future amendments.

Although the Olaparib CAEPR (Version update 2.3, June 18, 2018) and Amendment # 6 of NRG GY005 (August 14, 2018) indicate the events of 'platelet count decreased' as Insufficient Evidence, the MFDS of Korea noted that thrombocytopenia (or platelet count decreased) is "Less Likely" adverse event for the national approval of Olaparib and thus did not allow change to undefined (Insufficient Evidence) due to discrepancy. The MDFS cited submitted data and clinical data as well as foreign permits for this decision; 'thrombocytopenia' or 'platelet count decreased' of Olaparib capsules are common (≥ 1/100 to <1/10) according to European permit and has been reported to occur in > 25% of patients per US permit. It is aligned with the common adverse event (≥ 1/100 to <1/10) of the Korea national permits. Therefore, domestic permits will be submitted based on the core label (CDS) of AstraZeneca according to the domestic regulation and will be submitted after global approval.