SUMMARY OF CHANGES -- PROTOCOL

NCI Protocol #: 9984
Local Protocol #: 2000020461
Protocol Version Date: September 7, 2021

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with olaparib**.**

I. Request for Rapid Amendment Letter for Olaparib from CTEP on 8/27/21:

	Section	Comments

1.	7.1.1.2
	for Insertion of Revised CAEPR (Version 2.5, July 1, 2021), Page **67**
		• The SPEER grades have been updated.
		• Added New Risk:
		  • Rare but Serious: Allergic reaction; Febrile neutropenia; Skin and subcutaneous tissue disorders - Other (angioedema); Skin and subcutaneous tissue disorders - Other (erythema nodosum)
		  • Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution: Arterial thromboembolism; Atrial fibrillation; Death NOS; Dermatitis radiation; Enterocolitis; Erythema multiforme; Esophageal stenosis; Hypoxia; Muscle weakness upper limb; Obstruction gastric; Peripheral ischemia; Reversible posterior leukoencephalopathy syndrome; Sinus bradycardia; Soft tissue necrosis lower limb; Treatment related secondary malignancy
		• Increase in Risk Attribution:
		  • Changed to Likely from Less Likely: Abdominal pain
		  • Changed to Less Likely from Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution: Mucositis oral; Muscle cramp; Myalgia; Pain in extremity; Rash maculo-papular
		• Decrease in Risk Attribution:
		  • Changed to Rare but Serious from Less Likely: Platelet count decreased
		  • Changed to Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution from Less Likely: Fever; Lymphocyte count decreased
		• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:

		• Added to SPEER: Back pain; Neutrophil count decreased • Provided Further Clarification: • Infection listed under Less Likely is now captured as "Upper respiratory infection" and "Urinary tract infection" under Less Likely. PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.5, and associated risk information for the ICD, to the most recent CAEPR Version 2.4. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.4), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

II. Additional Changes

	Section	Comments
2.	Header, all pages	Version date updated
3.	Title Page	Version date updated.
4.	Title Page, Project manager	Project manager's contact information updated
5.	TOC	Table of Contents updated

Protocol #: 9984

Local Protocol #: 2000020461

ClinicalTrials.gov Identifier: NCT02893917

TITLE: A Randomized Phase 2 Study of cediranib in Combination with olaparib versus olaparib alone in men with metastatic castration resistant prostate cancer

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CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

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NCI-Supplied Agent(s): AZD2171 (cediranib) #NSC 732208; Olaparib (AZD2281) NSC 747856

IND #:

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Original/ Version 1 / Version Date: July 25, 2016
Revision/ Version 2 / Version Date: September 29, 2016
Revision/ Version 3 / Version Date: November 29, 2016
Amendment/ Version 1 / Version Date: January 23, 2017
Amendment/ Version 2/ Version Date: March 23, 2017
Amendment/ Version 3/ Version Date: September 14, 2017
Amendment/ Version 4/ Version Date: April 03, 2018
Amendment/ Version 5/ Version Date: May 17, 2018
Amendment/ Version 6/ Version Date: August 02, 2018
Amendment/ Version 7/ Version Date: January 7, 2019
Amendment/ Version 8/ Version Date: April 2, 2019 (Withdrawn by CTEP)

Amendment/ Version 9/ Version Date: May 28, 2019
Amendment/ Version 10/ Version Date: September 8, 2020
Amendment/ Version 11/ Version Date: September 7, 2021

SCHEMA

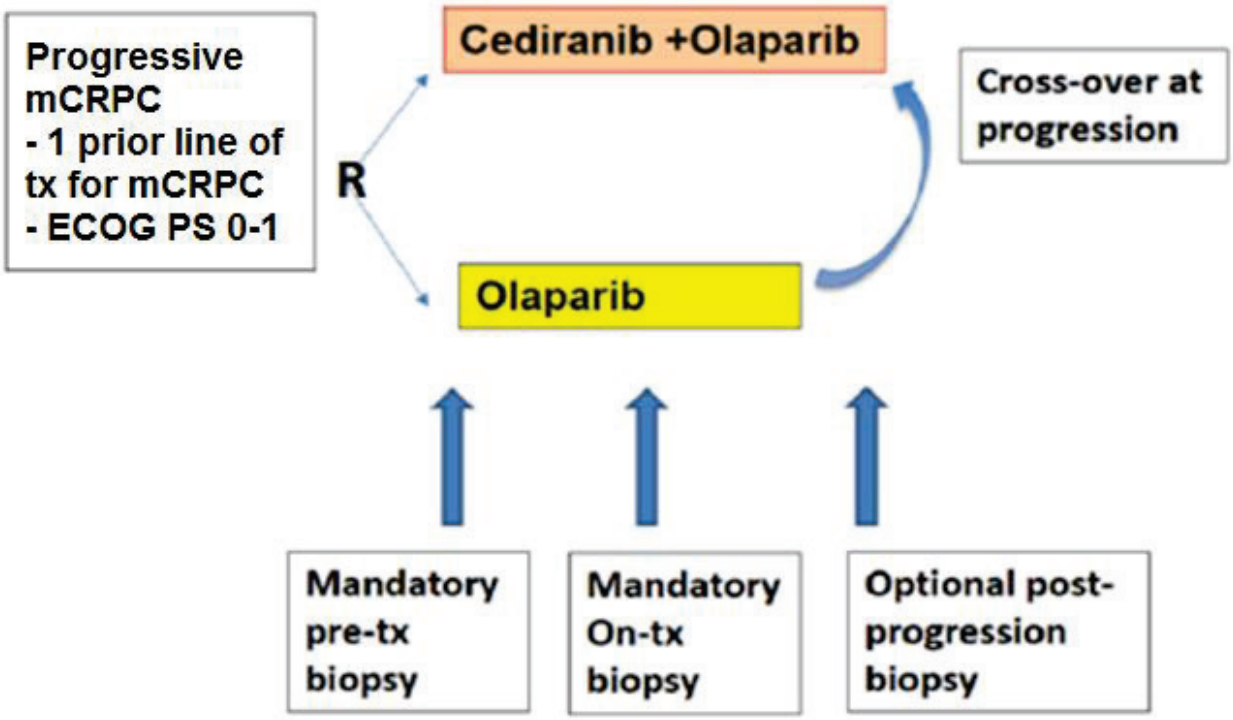

Progressive mCRPC
- 1 prior line of tx for mCRPC
- ECOG PS 0-1
R
Cediranib +Olaparib
Olaparib
Cross-over at progression
Mandatory pre-tx biopsy
Mandatory On-tx biopsy
Optional post-progression biopsy

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the clinical activity of the combination of cediranib and olaparib, as measured by radiographic progression free survival (rPFS), as compared to olaparib monotherapy in patients with mCRPC. See Section 11.1.7 for the definition of rPFS.

1.2 Secondary Objectives

1.2.1 To assess the clinical activity of the combination of cediranib and olaparib, as measured by PSA response rate, radiographic response rate by RECIST v1.1, and overall survival (OS), as compared to olaparib monotherapy in patients with mCRPC.

- PSA response is defined by PSA decline $\geq$ 50% from the baseline, confirmed by a second value 3-4 weeks later

1.2.2 To evaluate association of homologous recombination DNA repair deficiency (HRD) with the clinical activity of the combination of cediranib and olaparib or olaparib monotherapy, as measured by rPFS, in mCRPC patients.

- HRD positive status is defined by presence of homozygous deletion or deleterious mutations in key homologous recombination genes of DNA repair genes as analyzed by BROCA-HR test.

1.2.3 To evaluate the safety the combination of cediranib and olaparib and olaparib monotherapy in patients with metastatic prostate cancer.

1.3 Exploratory Objectives

1.3.1 To characterize genomic alterations by whole exome sequencing in mCRPC patients and correlate that with clinical activity or resistance to olaparib with or without cediranib

1.3.2 To characterize changes in RNA expression of DNA repair genes, angiogenesis markers, and immune markers, by whole transcriptome sequencing and correlate with clinical activity or resistance to olaparib with or without cediranib.

1.3.3 To characterize changes in immune tumor microenvironment in mCRPC patients by profiling expression of co-stimulatory and co-inhibitory molecules and tumor infiltrating lymphocytes, and correlate with clinical activity or resistance to olaparib with or without cediranib.

1.3.4 To identify baseline predictive biomarkers for rPFS or response and to identify on-treatment markers of acquired resistance in men with mCRPC receiving either olaparib plus cediranib or olaparib alone.

1.3.5 To explore biomarker signatures that correlate with the clinical activity or resistance to olaparib with or with cediranib, including changes in gene expression or acquired mutations in tumor biopsies.

2. BACKGROUND

2.1 Study Disease: Prostate Cancer

Metastatic castration resistant prostate cancer (mCRPC) is a disease that kills approximately 27,000 men each year in the United States (U.S.) alone [1]. It is the second leading cause of cancer-related death in the U.S. Approved therapies for mCRPC shown to confer survival benefit include sipuleucel-T, enzalutamide, abiraterone, docetaxel, radium-223 and cabazitaxel. Despite advancement of these new agents, resistance to these therapies is inevitably seen. Furthermore, the response to the subsequent hormonal therapy following abiraterone or enzalutamide, as an example, is only modest [2, 3]. One study suggests that the median overall survival among patients whose disease resistant to abiraterone or enzalutamide, via AR-V7 as an example, is in the range of 5.5 months to 10.6 months [4]

A systemic, multi-institutional study of clinical mCRPC tumors obtained from 150 men has provided genomic landscape data of mCRPC [5]. In that study, aberrations in *AR,* ETS genes, *TP53* and *PTEN* were the most frequent (40 to 60%). Of note, aberrations of *BRCA2, BRCA1* and *ATM* were observed in 19.3% overall, including 5.3% (8 of 150) harboring germline *BRCA2* mutations with a subsequent somatic event resulting in bi-allelic loss. Other recurrent aberrations in DNA repair genes were identified in at least 34 of 150 (22.7%). Recently, Prichard et al. also isolated germline DNA from 692 men with metastatic prostate cancer and reported that 82 men (11.8%) had deleterious germline DNA-repair gene mutations. The mutations were found in 16 genes, including *BRCA2* (5.3%), *ATM* (1.6%)*, CHEK2* (1.9%)*, BRCA1* (0.9%), *RAD51D* (0.4%) and *PALB2* (0.4%) [6]. Additionally, the clinical samples from a single-center phase II study (TOPARP) study in United Kingdom, reported that 16 of 49 (33%) mCRPC were found to have homozygous deletion and/or deleterious mutations in the genes of DNA repair pathway [7]. Other groups have also reported 12% (7 of 60) of advanced prostate cancers are hyper-mutated and have mutations in *MSH2* and *MSH6* mismatch repair genes [8]. In summary, it is estimated that about 12 to 33% of mCRPCs have defective DNA repair pathway. These findings are of special interest because agents targeting DNA repair pathway, notably, poly (ADP-ribose) polymerase (PARP) inhibitors, have shown promising activities in several solid tumors with defective DNA repair pathways.

2.2 CTEP IND Agents

2.2.1 Cediranib (AZD2171) (NSC 732208)

Cediranib (AZD2171) is a potent small molecule vascular endothelial growth factor

(VEGF) receptor tyrosine kinase (RTK) inhibitor of all three VEGF receptors (VEGFR-1, -2 and -3) at nanomolar concentrations. Inhibition of VEGF signalling leads to the inhibition of angiogenesis, lymphangiogenesis, neovascular survival and vascular permeability. Cediranib has additional activity against stem cell factor receptor (c-kit) tyrosine kinase inhibiting this kinase with a similar potency to that at which it inhibits VEGFRs. Cediranib is less active versus platelet-derived growth factor receptor (PDGFR) tyrosine kinases, and inactive against other kinases tested.

Cediranib inhibited the growth of tumours in preclinical models in a dose-dependent manner. At doses that reduce tumour growth VEGFR-2 and c-kit were inhibited, but only partial inhibition of PDGFR was observed. Anti-tumour activity was associated with a reduction in micro-vessel density and changes in vascular permeability. Cediranib reduced ascites accumulation in pre-clinical models of ovarian cancer. Cediranib also inhibited metastatic dissemination in pre-clinical models, and through inhibition of VEGFR-3 inhibited lymphangiogenesis. Collectively, these changes indicate that cediranib limits tumour growth, metastases and microvascular permeability. Following once daily (od) dosing with 20 mg cediranib, the unbound minimum steady-state plasma concentration (Css,min) was approximately 5-fold greater than the human umbilical vein endothelial cell (HUVEC) proliferation inhibitory concentration 50% (IC50) reported in non-clinical studies. At a clinical dose of 20 mg in patients, a small increase in diastolic blood pressure (DBP) and systolic blood pressure (SBP) is expected; a significant reduction in serum soluble VEGFR2 was observed; and a decrease in tumour vessel permeability and vascularity in liver lesions, as measured by dynamic contrast enhanced magnetic resonance imaging, was detected.

Preclinical, toxicology and safety, pharmacology and clinical experience is fully described in the current version of the cediranib investigator's brochure. (Cediranib IB Ed. 19)

2.2.1.1 Pharmaceutical information.

Refer to Section 8.1.1

2.2.1.2 Clinical Activity of Cediranib in Prostate Cancer:

Ryan et al reported the results of a phase I dose escalation and pharmacokinetic study of cediranib in patients with advanced prostate cancer [9]. Twenty-six patients received oral daily dosing of AZD2171 at 1, 2.5, 5, 10, 20, 30 mg. The maximum tolerated dose (MTD) was defined as the dose below that at which >or=33% of patients experienced a dose-limiting toxicity (DLT) within 21 days of initiating therapy. Pharmacokinetic analysis was performed. DLTs occurred at the 30 mg dose and included grade 3 events in three patients: fatigue (n = 3) and muscle weakness (n = 2). The pharmacokinetic profile revealed an effective half-life of approximately 27 h. At steady state, the unbound drug concentration was 4.4 times above the concentration required to inhibit endothelial cell proliferation in vitro. Four patients experienced PSA reductions within 30 days following drug discontinuation (one on 2.5 mg, two on 20 mg and 1 on 30 mg). In two patients treated with 20 mg, post therapy PSA declines persisted for >17 months, despite a PSA increase

on therapy. Resolution of adenopathy occurred in one patient persisting for >17 months. Plasma concentrations were maximum 2-8 h post dosing with an overall median value of 2 h. The dose of 20 mg daily was declared as the MTD. One objective response and several PSA declines following the discontinuation of therapy for toxicity suggest that evidence of clinical efficacy may be delayed. While further study is indicated, careful attention must be paid to the novel toxicities of this agent with prolonged dosing.

Dahut et al. reported the final data of a phase II study of cediranib in patients with docetaxel-pre-treated, castrate-resistant prostate cancer [11]. A total of 59 patients were enrolled, of whom 67% had received two or more previous chemotherapy regimens. Patients were treated with 20mg orally daily. Six of 39 patients with measurable disease had confirmed partial responses and one had an unconfirmed partial response. At 6 months, 43.9% of patients were progression-free; the median PFS and OS periods for all patients were 3.7 months and 10.1 months, respectively. The DCE-MRI variables baseline transport constant (Ktrans) and rate constant at day 28 were significantly associated with PFS in univariate analyses, but only baseline Ktrans remained significant when considered jointly. The most frequent toxicities were hypertension, fatigue, anorexia and weight loss; the addition of prednisone reduced the incidence of constitutional toxicities.

2.2.2 Olaparib (AZD2281) (NSC 747856)

Olaparib (AZD2281, KU-0059436) is a potent inhibitor of polyadenosine 5'diphosphoribose polymerase (PARP) developed as a monotherapy as well as for combination with chemotherapy, ionising radiation and other anti-cancer agents including novel agents and immunotherapy. The capsule formulation of olaparib was approved in December 2014 by the European Commission (EC) and United States (US) Food and Drug Administration (FDA), as follows:

> **EU indication**: Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.
>
> **US indication:** Lynparza is indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

The approved tradename for olaparib is LYNPARZA™.

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

Preclinical, toxicology and safety, pharmacology and clinical experience is fully described in the current version of the olaparib investigator's brochure. (Olaparib IB Ed. 14)

2.2.2.1 Pharmaceutical information

Please refer to Section 8.1.2

2.2.2.2 Clinical Activity of Olaparib in Prostate Cancer

Olaparib (Lynparza™) is indicated as monotherapy in patients with deleterious or suspected deleterious germline *BRCA* mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

The efficacy of Lynparza was investigated in a single-arm study in patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) advanced cancers (Study 1). A total of 137 patients with measurable, g*BRCA*m associated ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received Lynparza at a dose of 400 mg twice daily as monotherapy until disease progression or intolerable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator according to RECIST v1.1. The median age of the patients was 58 years, the majority were Caucasian (94%) and 93% had an ECOG PS of 0 or 1. Deleterious or suspected deleterious, germline *BRCA* mutation status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the companion diagnostic BRACAnalysis CDxTM, which is FDA approved for selection of patients for Lynparza treatment.

Efficacy results from the Study 1 are summarized in the Table below.

	N=137
Objective Response Rate (95% CI)	34% (26, 42)
Complete Response	2%
Partial Response	32%
Median DOR in months (95% CI)	7.9 (5.6, 9.6)

In January 2016, the US Food and Drug Administration (FDA) granted Breakthrough Therapy designation for olaparib for the monotherapy treatment of *BRCA*1/2 or *ATM* gene mutated metastatic Castration Resistant Prostate Cancer (mCRPC) in patients who have received a prior taxane-based chemotherapy and at least one newer hormonal agent (abiraterone or enzalutamide).

This designation was based on the results of the TOPARP-A Phase II trial [7]. The study showed that sixteen of 49 patients who could be evaluated had a response (33%; 95% confidence interval, 20 to 48), with 12 patients receiving the study treatment for more than 6 months. Next-generation sequencing identified homozygous deletions, deleterious mutations, or both in DNA-repair genes--including *BRCA*1/2, *ATM,* Fanconi's anemia

genes, and *CHEK2*--in 16 of 49 patients who could be evaluated (33%). Of these 16 patients, 14 (88%) had a response to olaparib, including all 7 patients with *BRCA2* loss (4 with biallelic somatic loss, and 3 with germline mutations) and 4 of 5 with *ATM* aberrations. The specificity of the biomarker suite was 94%. Anemia (in 10 of the 50 patients [20%]) and fatigue (in 6 [12%]) were the most common grade 3 or 4 adverse events, findings that are consistent with previous studies of olaparib.

2.3 Rationale

A systemic, multi-institutional study of clinical mCRPC tumors obtained from 150 men has provided genomic landscape data of mCRPC [5]. In that study, aberrations in *AR,* ETS genes, *TP53* and *PTEN* were the most frequent (40 to 60%). Of note, aberrations of *BRCA2, BRCA1* and *ATM* were observed in 19.3% overall, including 5.3% (8 of 150) harboring germline *BRCA2* mutations with a subsequent somatic event resulting in bi-allelic loss. Other recurrent aberrations in DNA repair genes were identified in at least 34 of 150 (22.7%). Recently, Prichard et al. also isolated germline DNA from 692 men with metastatic prostate cancer and reported that 82 men (11.8%) had deleterious germline DNA-repair gene mutations. The mutations were found in 16 genes, including *BRCA2* (5.3%), *ATM* (1.6%)*, CHEK2* (1.9%)*, BRCA1* (0.9%), *RAD51D* (0.4%) and *PALB2* (0.4%) [6]. Additionally, the clinical samples from a single-center phase II study (TOPARP) study in United Kingdom, reported that 16 of 49 (33%) mCRPC were found to have homozygous deletion and/or deleterious mutations in the genes of DNA repair pathway [7].

Other groups have also reported 12% (7 of 60) of advanced prostate cancers are hyper-mutated and have mutations in *MSH2* and *MSH6* mismatch repair genes [8]. In summary, it is estimated that about 12 to 33% of mCRPCs have defective DNA repair pathway. These findings are of special interest because agents targeting DNA repair pathway, notably, poly (ADP-ribose) polymerase (PARP) inhibitors, have shown promising activities in several solid tumors with defective DNA repair pathways.

PARP is a large family of proteins involved in multiple cellular process including DNA repair, chromatin regulation, transcription regulation, apoptosis and others [10]. As a regulator of transcription factor, PARP-1 elicits pro-tumorigenic effects in androgen receptor (AR)-positive prostate cancer cell lines, regardless of the genotoxic insult [11]. PARP1 is recruited to sites of AR function, therein promoting AR occupancy and supporting transcriptional function. In vivo, PARP inhibitor has shown anti-tumor activities both in, hormone sensitive and hormone resistant PC models [11]. Additionally, Brenner et al has demonstrated the role of PARP1 in ETS gene –mediated transcription and cell invasion in preclinical models of prostate cancer. Inhibition of PARP has resulted in inhibition of ETS positive prostate cancer xenograft growth [12].

Olaparib, PARP inhibitor, in prostate cancer: Recently, the data from a phase II trial of olaparib in 49 men with mCRPC (TOPARP study) were presented at the 2015 Annual Meeting of AACR by Mateo and his colleagues [13]. Olaparib 400mg twice a day was overall well tolerated without any unexpected side effects in this heavily pre-treated patients. The two most common toxicities were anemia (76%) and fatigue (58%). Twenty-six percent of the patients required a dose reduction to 300mg bid. The response data

indicated that olaparib is active as a monotherapy in a significant subgroup of patients. Sixteen of 49 (32.7%) unselected patients achieved response defined by PSA decline >50%, objective response and/or CTC conversion. A post hoc analysis to explore the biomarker of response from the tumor biopsy tissue suggested that the markers of DNA repair defect appear to be a potential biomarker of response. The biomarkers were defined by homozygous deletion and/or a putative deleterious mutation in a gene reported to be involved in DNA repair and /or sensitivity to PARP inhibition. In this study, 16 (32.7%) patients had biomarker positive and 33 (67.3%) patients were biomarker negative. Among the 16 responders, 14 of these patients were noted to have a biomarker and 2 responders did not have a biomarker. Homozygous deletion or deleterious mutation in *BRCA2* and *ATM* were the most commonly observed events associated with response to olaparib. Other affected genes associated with response include *FANCA, CHEK2, BRCA1, PALB2, HDAC2, RAD51, MLH3, ERCC3, MRE11,* and *NBN.*

Hypoxia-induced downregulation of DNA repair genes

Hypoxia is one of the characteristics of the microenvironment in a growing tumor. Inadequate vascularization in tumors creates a microenvironment that is low in oxygen supply, rendering tumors hypoxic. Tumors respond to this condition by inducing angiogenesis, mainly through VEGF-dependent pathways [14]. Multiple are the changes that a tumor cell must undergo to survive the metabolic challenges imposed by a low oxygen state. Hypoxia-inducible factor 1alpha (HIF-1α) is primarily responsible for alterations in metabolism that support the survival of hypoxic tumor cells. Among many others, hypoxia has been shown to confer cancer cells several adaptive survival mechanisms, including increased glycolysis, angiogenesis, metastasis, EMT, resistance to radiation therapy and chemotherapy.[14-16]

Dr. Peter Glazer's laboratory at Yale University tested a hypothesis that genomic instability is one of the tumor's genomic adaptions to hypoxia. His lab and other groups demonstrated that hypoxia induces homologous recombination DNA repair defects by transcriptional repression of *RAD51, BRCA1* and *BRCA2* in multiple cancer cell lines including MCF7 (breast), A549 (lung adenocarcinoma), RKO (colon), CaCo-2 (colon), PC3 (prostate) and DU145 (prostate) [17]. In addition, Dr. Robert Bristow's laboratory at University of Toronto also demonstrated that hypoxia down-regulates DNA repair genes, including HR-related genes (*Rad51, Rad52, Rad54, BRCA1, BRCA2)* and NHEJ-related genes (*Ku70, DNA-PKcs, DNA ligase IV, XRCC4)* in prostate cancer cells [18]. Subsequent work also reported that PARP inhibitors exerted increased cytotoxicity against multiple cancer cells under hypoxic conditions, compared to normoxic conditions [19]. Posttranslational modifications of histones have been described as an important epigenetic

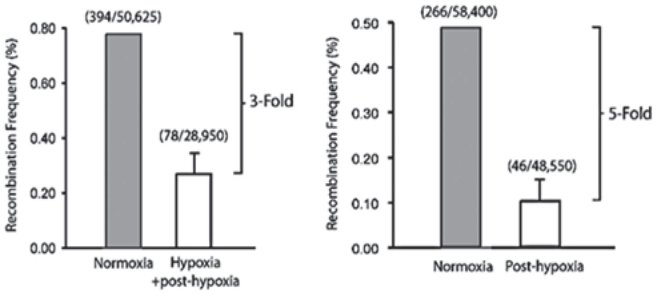


Figure 1: Decreased homologous recombination (HR) in hypoxic and post-hypoxic cells (Bindra RS. 2005. Annals of the NYAS)

mechanism of gene regulation [20-22]. Hypoxia also drives epigenetic modification of the BRCA1 promoter via decreases in methylation of H3K4 as well as combined decreases in acetylation/ increased methylation of H3K9 [23]. Similar modifications are seen during the downregulation of the RAD51 promoter in hypoxic conditions and the same epigenetic mechanism is involved in the upregulation of VEGF in hypoxia [23], that is thought to trigger angiogenesis. Taken together, hypoxia-induced downregulation of DNA repair genes may have therapeutic implications for the use of PARP inhibitors.

Cediranib: a pan-VEGFR tyrosine kinase inhibitor and an inducer of tumor hypoxia

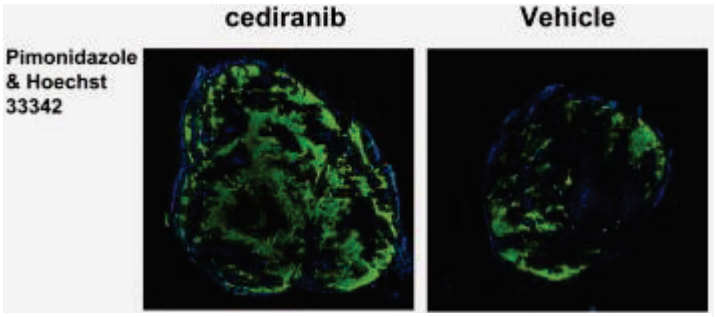


Figure 2: Representative composite images of pimonidazole adduct (green, hypoxia) and Hoechst 33342 (blue, perfusion) uptake in cediranib- or vehicle treated rat C6 gliomas (Burrell JS et al. IJC 2012)

Cediranib is a potent tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3. Cediranib has been shown in preclinical models to inhibit vascular permeability and perfusion as measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) [24-26]. An imaging biomarker study in a xenografts model demonstrated that cediranib treatment led to tumor hypoxia and decreased perfusion as shown in **Figure 2** above [27]. In another study using HT29 colorectal xenografts model, the tumor response to short-term treatment with cediranib (3 daily doses) was also studied using dynamic contrast-enhanced and diffusion weighted MRI as well as ^{18}F-fluoromisonidazole (^{18}F-FMISO) (hypoxia imaging) positron emission tomography (PET) and histological markers. Rats bearing human tumor xenografts were imaged at baseline and 2 hours after the final dose of cediranib. DCE-MRI-derived parameters decreased significantly in cediranib treated animals compared to controls. The fraction of perfused blood vessels in the cediranib-treated group was lower than the control group. Treatment with cediranib showed decreased post-treatment ^{18}F-FMISO uptake, suggesting that short-term treatment with cediranib caused decreases in tumor permeability and perfusion and induced hypoxia [28]. Histological assessments of tumor xenografts from animals, in which cediranib significantly delayed tumor growth, revealed reduced vessel density and perfusion as well as increased hypoxia on cediranib treatment, which was enhanced by concomitant radiation treatment [29].

Cediranib in Prostate cancer

The activity of cediranib has been demonstrated in two early phase clinical trials. A phase I dose escalation study of cediranib in 26 patients with hormone refractory prostate cancer indicated that the 20mg daily dose was the maximally tolerated dose (MTD) [9]. The most frequently occurring AEs were fatigue, dysphonia, headache, hypertension, diarrhea, and anorexia. In that study, favorable PSA changes and a durable objective response have been noted. In a phase II study, cediranib 20mg a day resulted in objective responses in 6 of 39 patients (15%) with mCRPC who had prior docetaxel-based therapy [30]. The data

indicated a lack correlation between objective responses and PSA changes. Additionally, the imaging biomarker study with DCE-MRI suggested that cediranib has a direct effect on the microcirculation and vasculature. PSA levels have not corresponded with imaging responses.

Clinical Data on Combination of Cediranib and Olaparib
A phase I study of the cediranib and olaparib was tested in 28 patients with recurrent ovarian or triple-negative breast cancer at 4 dose levels. Two dose limiting toxicities were observed (One grade 4 neutropenia $\geq$ 4 days and the other grade 4 thrombocytopenia, occurred at the highest dose level (cediranib 30mg once daily and olaparib 400mg twice daily. The RP2D was cediranib 30mg once a day and olaparib 200mg twice a day [31]. A randomized phase II study of the combination versus olaparib in patients with platinum-sensitive ovarian cancer showed a statistically significant improvement in median progression-free survival (17.7 vs 9.0 months; hazard ratio 0.42, 95% CI 0·23-0·76; p=0·005). Grade 3 and 4 adverse events were more common with combination therapy than with monotherapy, including fatigue, diarrhea, and hypertension.

Rationale for Cediranib Olaparib Combination Dosing
This study will use the recommended phase II dosing from phase I study by Joyce Liu et al: oral administration of cediranib 30mg once a day in combination with olaparib 200mg twice a day, continuously[31].

Unlike the earlier safety studies, Liu's Phase I study and the subsequent studies have implemented much more stringent guideline (See Section 6) on management of the toxicities related to the cediranib and olaparib combination, such as hypertension management with daily monitoring of blood pressure, and early initiation of anti-hypertensive. Such strategies have significantly helped management of the toxicities and the doses of up to 30mg of cediranib and olaparib 200mg bid were well tolerated with manageable side effects.

In addition, the study will use mobile application, eCediranib-Olaparib (eCO) Application, to monitor patients' side effects, such as hypertension and diarrhea. This application will allow the investigators to allow therapeutic interventions and drug holidays to allow optimal management of the side effects.

Rationale for Olaparib tablet monotherapy dose
The current US FDA approval of olaparib in ovarian cancer is 400mg of olaparib capsules twice a day. Sixteen olaparib capsules per day are required the approved 400mg twice-daily dose. To that end, a tablet formulation has been developed to reduce pill burden and has been studied in several clinical trials for optimal dose and administration scheduled of the tablet formulation.

Specifically, in prostate cancer, Mateo et al reported the bioavailability study [32]. Olaparib 200 mg tablets displayed similar Cmax,ss, but lower AUCss and Cmin,ss than 400 mg capsules. Following multiple dosing, steady-state exposure with tablets ≥300 mg matched or exceeded that of 400 mg capsules. After dose escalation, while 400 mg twice

daily was the tablet maximum tolerated dose based on hematological toxicity, 65 % of patients in the randomized expansion phase eventually required dose reduction to 300 mg. Intermittent tablet administration did not significantly improve tolerability. Tumor shrinkage was similar for 300 and 400 mg tablet and 400 mg capsule cohorts. The authors concluded that they recommended that 300mg twice daily was the recommended monotherapy dose of olaparib tablet.

Summary of rationale for the combination of cediranib and olaparib for prostate cancer

1. A significant proportion of advanced mCRPCs harbor mutations in DNA repair pathways.
2. Olaparib has shown anti-tumor activities in patients with mCRPC, mostly limited to patients with the tumors harboring mutations in DNA repair pathways.
3. Cediranib, by inducing tumor hypoxia, may result in downregulation of the DNA repair genes leading to sensitization of the tumor to olaparib, a PARP inhibitor, in patients with mCRPC.
4. Combination of cediranib 30mg once a day, and olaparib 200mg BID has well documented and manageable toxicity profile.
5. The combination has demonstrated superior clinical outcome compared with olaparib monotherapy in patients with advanced ovarian cancer.

Hypothesis: The combination of cediranib and olaparib has superior clinical activity, as measured by radiographic progression free survival, in patients with mCRPC, compared with olaparib monotherapy.

2.4 Correlative Studies Background

2.4.1 BROCA-HR Panel (**Dr Elizabeth Swisher, University of Washington, Seattle) (Integrated Biomarker)**

The BROCA-HR assay will be used in the study to assess correlation of homologous recombination deficiency (HRD) status, on the effectiveness of cediranib/olaparib combination and olaparib monotherapy.

BRCA1 and *BRCA2 (BRCA1/2*) are tumor suppressor genes, in which inherited loss-of-function mutations confer a high lifetime risk of breast and ovarian carcinoma. *BRCA1/2* are key components of the BRCA-Fanconi anemia (FA) pathway, which is critical to homologous combination-mediated DNA repair. Other genes in this pathway (*BRIP1/FANCJ, PALB2/FANCN, RAD51C/FANCO, RAD51D*) also contribute to hereditary breast and ovarian cancer [33-37]. The Cancer Genome Atlas Network (TCGA) recently suggested that up to half of serous ovarian carcinomas have homologous recombination defects (HRD), but that estimate was based on a variety of molecular findings, many with uncertain impact on DNA repair function [38]. PARP inhibitors (PARPi) demonstrate synthetic lethality in cells with HRD, including cells deficient in *BRCA1/2* [39, 40]. Recurrent ovarian carcinomas in *BRCA1/2* mutation carriers have an approximate 40% response rate to PARPi and also have an increased response to platinum based chemotherapy [41]. Importantly, approximately 25% of serous ovarian cancers that

are wildtype for *BRCA1/2* also respond to PARPi [42].

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 ovarian carcinomas [38, 43] and also appear to confer sensitivity to PARPi [44]. PARPi also selectively kill cells *in vitro* that are deficient in other (HR) genes including *RAD51D, NBN, ATM,* and *CHEK2* [33, 45]. 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 [43].

In order to respond to a PARPi, cancer cells need to be deficient in HR but also proficient in the alternative error prone non-homologous end joining (NHEJ) DNA repair pathway [46, 47]. Thus, loss of HR is not, by itself, sufficient for PARPi sensitivity, and an accurate predictor of PARPi responsiveness could require assessment of many components of both the HR and NHEJ pathways. A more efficient assay, which would not require a prior knowledge of the critical elements in these DNA repair pathways, would instead measure DNA repair capacity. Recent evidence suggests that *BRCA1/2* deficient cancers exhibit global DNA alterations termed "genomic scarring" that are consistent with their reliance on the NHEJ pathway [48-50]. This genomic scar could serve as a downstream measure of 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.

The marked susceptibility of patients with gBRCAm-associated cancers has validated gBRCAm as a predictive biomarker for PARPi response [51]. Other mechanisms of HRD may be a functional biomarker for response to DNA damaging agents and PARPi. Thus, it may be important to identify which 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 cancer patients with HRD, and may yield biomarkers with potential to guide administration of this combination therapy.

BROCA is a targeted capture and massively parallel sequencing assay that is capable of identify all classes of mutations including gene rearrangements [52, 53]. 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 [54]. 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) [54, 55].* 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) [56]. The presence of either a germline or somatic FA/HR mutation is highly predictive of an improved primary response to platinum chemotherapy and longer

overall survival [56]. Germline and somatic loss of function mutations were identified in all of the 13 FA/HR genes evaluated.

Dr. Swisher's laboratory has designed a new version of BROCA (BROCA-HR) that includes many additional DNA repair genes (75 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 PARPi such as *TP53BP1* [57-59]. The current design for BROCA-HR includes the following genes:

BROCA-HR gene list (n=75)

a. FA-BRCA HR pathway: *ATM, ATR, BABAM1, BAP1, BARD1, BLM, BRCA1, BRCA2 (FANCD1), BRIP1 (FANCJ), BRCC3, BRE, CHEK1, CHEK2, ERCC1, ERCC4 (FANCQ), FAM175A (abraxas), FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG (XRCCC9), FANCI, FANCL, FAMCM, GEN1, MRE11A, NBN, PALB2 (FANCO), RAD50, RAD51C (FANCO), RAD51D, RBBP8 (CtIP), SLX4 (FANCP), UIMC1 (RAP80), XRCC2*
b. DNA mismatch repair *MLH1, MSH2 (*and *EPCAM), MSH6, PMS2*
c. Other DNA repair, surveillance genes, or modifier genes : *CDK12*, *CDH4*, *HELQ, NEIL1, PPM1D, POLD1, POLE, RIF1,TP53, ID4, PAXIP1, POLQ, RINT1, TP53BP1, USP28, WRN, XRCC3*
d. NER genes: *ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, DDB1, XPA, XPC*
e. NHEJ genes: *DCLRE1C, LIG4, PRKDC, TOBP1, XRCC4, XRCC5, XRCC6*
f. PI3K pathway: *PTEN, PI3KCA*

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. The theoretical ability of 3000 SNPs to define "genomic scarring" in existing TCGA data was tested by Dr. Swisher's lab (unpublished data). Using only 3000 SNPs can define cases with high LOH which have better prognosis. Combining the BRCA mutational status and the LOH profile provides additional prognostic information.

In this trial, 3000 SNPs will be assayed in the same BROCA-HR mutational assay at no additional cost which will provide an LOH profile to assess genomic scarring as an exploratory biomarker. The mutation information from BROCA sequencing will then be combined with the LOH profile to test performance of a combined biomarker, with the prediction that HR proficient cancers may achieve less benefit from the addition of PARPi.

Cases will be identified as HR proficient or deficient based on sequencing data of known Fanconi anemia (FA)-BRCA genes.

2.4.2 Whole Exome Sequencing (Dr. Eli Val Allen, Broad Institute / Dana Farber Cancer Institute), **Integrated Biomarker**

The Sequencing Platform of the Broad Institute boasts 50 Illumina HiSeq instruments and 10 MiSeqs, for an average capacity of 2.1 Terabytes (spanning 6192 flow cells) per day.

The Broad developed the leading commercial method for whole-exome solution-phase hybrid selection (now licensed to Agilent). This approach to hybrid selection has now been widely adopted by major companies and other centers and has been used in > 100 publications. The whole-exome panel includes: 18,557 genes (selected from RefSeq CDS) comprising 185,915 exons and 33 Mb of target. These targets are covered by 277,944 oligo "baits". A new exome-wide bait set is being adapted that allows more even sequence coverage per capture reaction; this innovation will allow us to sequence clinical tumor samples to a sufficient overall mean coverage, while preserving the overall sensitivity and specificity of variant calling at a reduced cost.

To perform WES, nucleic acid (DNA and RNA) will be obtained from tumor cellular material using SOPs in common use at the Broad Biological Samples Platform. Nucleic acid will be transferred to the Genetic Analysis Platform at the Broad Institute. DNA quality and quantity will be confirmed by gel electrophoresis and Picogreen, respectively. The tumor and normal exome will be selected using the solution-phase hybrid capture method, and sequencing will be performed using the Illumina HiSeq, HiSeq2500, or HiSeqX10 instrument (when the latter becomes available). For clinical tumor specimens, we will utilize a "high-coverage" sequencing approach, which should yield an average coverage of 150-200 fold; paired normal DNA will be sequenced to a depth of ~80-100-fold. WES data will be analyzed for base mutations, small insertions/deletions, and copy number alterations using the Firehose pipeline.

We evaluate our exome sequencing in a number of ways. First, it is critical to obtain even and robust coverage across targets, avoiding inefficiencies due to targets being at very different concentrations, or missing in one sample to the next. In the course of our exome development, we have found the following to be the most useful parameters to inform our coverage model and the most critical to optimize around to increase efficiency:

Non-duplicate reads. Observation of duplicate reads (reads with the same start and stop sites) indicates that the same molecule has been sequenced multiple times. This can mislead SNP calling algorithms, since the same molecule-specific (PCR or other) error can erroneously be counted as independent observations.

On-target sequence yield. A major inefficiency of all massively parallel targeting approaches is the inability to precisely and uniquely capture (to the base pair) the target of interest. Optimization of our protocol has resulted in routine on-target proportion of ~ 85% of reads.

Uniformity of coverage. All target enrichment methods are non-uniform (compared to whole genome shotgun). We measure non-uniformity using a metric - "fold-80 penalty". This represents the fold difference between the mean coverage for all targets and the coverage achieved by 80% of targets. That is, how much coverage must be increased so that 80% of targets achieve the mean coverage. In our experience, an increase of 3-5 fold is required with current protocols to ensure that 80% of target bases are covered to 30X.

Knowledge of these parameters is required to estimate the total sequence required in whole exome sequencing. We base our estimate on (a) target size of 30 Mb, (b) on-target rate of 80%, (c) desired coverage of 30X, and (d) a uniformity factor of 4 (80% of target achieves 30X). This model we estimate ~4.5 Gb of high quality, non-duplicate sequence per sample (30 Mb* 1.25 * 30 X * 4 = 4.5 Gb

2.4.3 Whole Transcriptome Sequencing (Dr. Eli Val Allen, Broad Institute / Dana Farber Cancer Institute, **Integrated Biomarker)**

In parallel with whole exome sequencing, the Broad Genomics Platform will perform whole transcriptome sequencing. The Broad Genomics Platform has extensive experience with whole transcriptome sequencing from both frozen and FFPE tumor samples. Regarding the latter, transcriptome capture is an alternative to traditional tran¬script enrichment methods (including polyA selection and ribosomal depletion) that is optimal for low-input and de-graded samples including formalin-fixed paraffin-embed¬ded (FFPE) tissues. The approach first prepares a stranded cDNA library from isolated RNA, then hybridizes the library to a set of DNA oligonucleotide probes to enrich the library for mRNA transcript fragments. Transcriptome Capture targets 21,415 genes, representing 98.3% of the RefSeq exome. Specific details on the sequencing methodology follow:

RNA samples and two positive controls (K-562) are assessed for quality using Agilent's Bioanalyzer 2100. The percentage of fragments with a size greater than 200nt (DV200) was calculated using the Agilent software. Samples with a DV200 score less than 30% were not included, as the likelihood of success is dramatically reduced with these more fragmented samples (see Illumina tech note: http://www.illumina.com/documents/products/technotes/technote-truseq-rna-access.pdf). 100ng of RNA is used as the input for first strand cDNA synthesis using Superscript III reverse transcriptase (Life Technologies, Cat. #18080044) and Illumina's TruSeq Stranded

Total RNA Sample Prep Kit (Illumina, Cat. #RS-122-2201). The fragmentation step prior to cDNA synthesis was omitted in the FFPE RNA samples, only the K-562 positive control samples were fragmented at 94°C for 8 minutes. Synthesis of the second strand of cDNA was followed by indexed adapter ligation. Subsequent PCR amplification enriched for adapted fragments. The amplified libraries are quantified using a Qubit assay (Life Technologies, Cat. #Q3285) and assessed for quality on an Agilent Technologies 2100 Bioanalyzer (DNA 1000 chip). 200ng of each cDNA library, not including controls, are combined into two 4-plex pools. Illumina's Coding Exome Oligos (Illumina, Part #15034575) that target the exome are added, and hybridized on a thermacycler with the following conditions: 95°C for 10 minutes, 18 cycles of 1 minute incubations starting at 94°C, then decreasing 2°C per cycle, then 58°C for 90 minutes. Following hybridization, streptavidin beads were used to capture the probes that were hybridized in the previous step. Two wash steps effectively remove any non-specifically bound products. These same hybridization, capture and wash steps are repeated to assure high specificity. A second round of amplification enriches the captured libraries. qPCR (Kapa Biosystems, Cat. #KK4600) was performed on the pooled libraries and normalized to 2nM. The normalized, pooled libraries were loaded onto HiSeq2500 for a target of 50 million 2x76bp paired reads per sample.

2.4.4 **Plasma Angiome (Integrated Biomarker, Dr. Andrew Nixon at Duke University)**

The focus of the blood-borne biomarkers across all study arms will be VEGF-A (VEGF), as VEGF expression is directly regulated by hypoxia through similar mechanisms as BRCA1 expression, however VEGF is induced, while BRCA1 is repressed. VEGF increases have been observed on treatment with cediranib in multiple studies and it is now accepted as a well-established PD marker, as increases have also been observed with other VEGF signaling inhibitors. In this study, VEGF will serve as an internal control for the effects of cediranib and hypoxia induction, which will be correlated to imaging endpoints and other hypoxia markers, as well as clinical efficacy.

In addition to VEGF, a panel of other co- and counter-regulated markers of angiogenesis and inflammation will be evaluated to identify potential prognostic and predictive biomarkers. Additionally, markers will be correlated with one another to identify biologically important patterns of expression among the analytes tested.

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 and validated assays, limited sample collection in most trials, in particular large randomized studies. 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 may be facilitated.

Recently, Dr. Nixon's multiplex ELISA approach has identified several strong candidate predictors of benefit from bevacizumab. In CALGB80303, a phase III study of gemcitabine

± bevacizumab, his group identified VEGF-D as a candidate predictor for benefit from bevacizumab [60]. Another recent and instructive success is the identification of IL-6 as a strong candidate predictive biomarker for anti-VEGF therapy in renal cell carcinoma. This marker was found to be a predictive marker in two independent phase III studies, each of which used a different VEGF inhibitor. VEG105192 was a phase III study of BSC +/- pazopanib in refractory mRCC [61] and CALGB90206 was a phase III study of IFN +/- bevacizumab in 1st line mRCC [62]. Both of these studies found that high levels of IL6 predicted for greater benefit from these VEGF inhibitors [63, 64]. The CALGB study with bevacizumab also found a predictive role for HGF that was IL-6 dependent (i.e., a 3-way treatment interaction) [63]. The role of the IL6-Jak-Stat axis is particularly intriguing given its role in tumor associated inflammation and anti-tumor immunity. Numerous other inflammatory mediators have been shown to regulate tumor angiogenesis and sensitivity to anti-VEGF therapy [65, 66]. Tumor angiogenesis, inflammation, and anti-tumor immunity have highly interconnected biologies, a topic that has been extensively reviewed [67-69]. However, to date, these factors have not been systematically interrogated in most anti-VEGF therapy trials. Analysis of the role of inflammation in mediating resistance to anti-VEGF therapy may be highly clinically relevant.

The design of the Dr. Nixon's multiplex panel array to interrogate diverse biologies related to angiogenesis is highly refined, technically robust and readily adaptable to clinical practice. Many of the analytes in the multiplex array were developed specifically for this use and have been carefully optimized for performance in plasma and serum samples from cancer patients. This approach utilizes the CiraScan™ platform from Aushon BioSystems Inc. The Nixon lab has worked in tandem with the team at Aushon for over eight years to develop multiple new assays and optimize the performance of the specific panel design (see Table 2.3).

While the markers listed below represent the most optimized panel to date, it is anticipated that new information and novel findings will be available at the time of analysis. The final decision on the specific markers to be evaluated will made using the most up-to-date information and best science available at the time of analysis.

Table 2.3 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	TGFβ1	IL-6
IGFBP1	VEGF-D	TGFβ2	PAI-1 Active
IGFBP2	sVEGFR1	TGFβRIII	PAI-1 Total
IGFBP3	sVEGFR2	TIMP1	SDF-1
PDGF-AA	sVEGFR3	TSP2	VCAM-1

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed progressive, metastatic castration resistant prostate adenocarcinoma by meeting **ALL** the following:

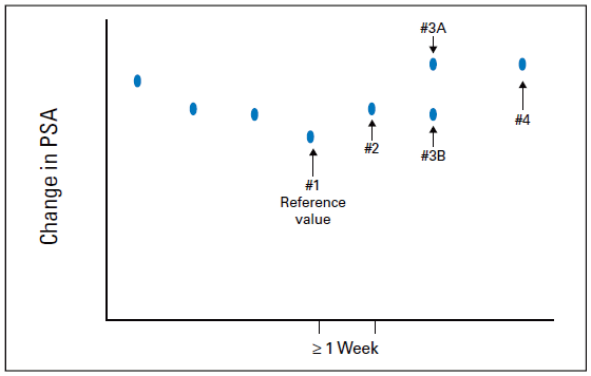
3.1.1.1 Pathology of prostate gland or metastatic disease must confirm the diagnosis of prostate adenocarcinoma. Mixed histology with other variants including but not limited to small cell or neuroendocrine differentiation must be discussed with the Study PI.

3.1.1.2 Metastasis must be documented by radiographic evidence.

3.1.1.3 Castration resistance must be documented with surgical or medical castration with serum testosterone <50ng/dL (<2.0 nM). If the patient is being treated with LHRH agonists (patient who has not undergone orchiectomy), this therapy must have been initiated at least 4 weeks prior to Cycle 1, Day 1 and must be continued throughout the study.

3.1.1.4 Progression must be evidenced and documented by any of the following parameters.

- Two consecutively rising PSA values, above the baseline, at a minimum of 1-week intervals. The minimal value to enter the study is 1.0 ng/ml or greater. The reference value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point 3 (value #3A) is greater than that at point 2, then eligibility has been met. If the PSA is not greater than point 2 (value #3B), but value #4 is, the patient is eligible assuming that other criteria are met, if values 3A or #4 are 1 ng/mL or higher (Prostate cancer Working Group 3. Scher HI et al. *J Clin Oncol.* 2016),



- Appearance of one or more new lesions on bone scan.
- Progressive disease by RECIST 1.1

3.1.2 Must have a tumor lesion safely accessible for biopsy per the investigator's discretion. While a soft tissue metastasis preferred for a biopsy, a bone metastasis is allowed for biopsy as long as enough cores can be obtained. A biopsied lesion cannot be used for target lesion for response assessment.

3.1.3 Must be agreeable to the mandatory research tumor biopsies (pre-treatment and on-treatment). Tumor biopsies are mandatory at pre-treatment and at on-treatment. There is an optional biopsy at post-progression.

3.1.4 Must have received at least one prior line of therapy for mCRPC. A taxane chemotherapy administered for metastatic castration sensitive disease will not count, unless patient develops disease progression within 12 months from the last dose chemotherapy.

3.1.5 Must have a life expectancy greater than or equal to 16 weeks.

3.1.6 If patient is currently on prednisone or other corticosteroids for palliation, the dose must be less than or equal to 10mg a day or its equivalent dose and it must have been started at least 4 weeks prior to cycle 1 day 1.

3.1.7 Patients must have measurable disease by RECIST v1.1, or evaluable disease with bone metastases demonstrated by Tc99 Bone Scan. See Section 11 for the evaluation of measurable disease. Patients with **bone metastases only** are allowed. (NOTE: Nodes ≥ 1.5cm (not ≥2cm) in the short axis are considered measurable, per PCWG3).

3.1.8 Toxicities of prior therapy (except alopecia) should be resolved to ≤ grade 1 as per NCI-CTCAE v5.0. Patients with long-standing stable grade 2 neuropathy or others (e.g., adrenal insufficiency or hypothyroidism on stable doses of replacement therapy) may be allowed after discussion with the study Principal Investigator (PI).

3.1.9 Age ≥18 years. There is no dosing or adverse event data currently available on the use of cediranib or olaparib in patients <18 years of age, thus excluding them from enrollment.

3.1.10 ECOG performance status 0 or 1 (Karnofsky ≥70%, see Appendix A).

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

3.1.11.1 WBC >3x10^9/L

3.1.11.2 Absolute neutrophil count ≥ 1,500/mcL

3.1.11.3 Platelets ≥ 100,000/mcL

3.1.11.4 Hemoglobin ≥10 g/dL with no pack red blood cell transfusion in the past 28 days

3.1.11.5 Creatinine Clearance ≥ 51mL/min, calculated using Cockcroft-Gault formula as follows: Cockcroft-Gault CrCl = (140-Age)* (Wt in Kg)/ (72*Cr)

3.1.11.6 Urine protein: creatinine ratio (UPC) of ≤ 1.

3.1.11.7 Total bilirubin ≤ 1.5x the institutional ULN

3.1.11.8 AST (SGOT) and ALT (SGPT) < 3 times institutional ULN unless liver metastases are present in which case they must be < 5 x ULN.

3.1.11.9 Coagulation parameters (INR and aPTT) within 1.25 × ULN institutional limits, except where a Lupus anti-coagulant has been confirmed, or except patients on anticoagulation.

3.1.12 Patients must be able to swallow oral medications and not have gastrointestinal illnesses that would preclude absorption of cediranib or olaparib.

3.1.13 Adequately controlled thyroid function, with no symptoms of thyroid dysfunction. Patients can be on thyroid hormone replacement medication. Asymptomatic patients with elevated TSH with normal T4/T3 are allowed to enroll, and recommended to follow with routine thyroid function test especially if they are randomized to cediranib/olaparib arm.

3.1.14 Adequately controlled blood pressure (BP) <140 mmHg (systolic) and <90 mmHg (diastolic) taken in the clinic setting by a medical professional within 2 weeks prior to starting study. Patients with hypertension may be managed with up to a maximum of 3 antihypertensive medications. Patients who are on 3 antihypertensive medications are highly recommended to be followed by a cardiologist or blood pressure specialist for management of BP while on protocol.

3.1.15 Patients must be willing and able to check and record daily blood pressure readings when randomized to cediranib containing arm.

3.1.16 Patients must have documented LVEF by echocardiogram greater than institution's lower limit of normal (or 55% if threshold for normal not otherwise specified by institutional guidelines) obtained within 3 months prior to registration **if** they have any of the following risk factors for cardiac toxicities:

- A New York Heart Association (NYHA) classification of II controlled with treatment (see Appendix B)
- Prior central thoracic radiation therapy (RT), including RT to the heart
- History of myocardial infarction within 12 months prior to registration.
- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- Prior history of other significant impaired cardiac function

3.1.17 Male participants and their female partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination [see below for acceptable methods], and not to donate sperm, throughout the period of taking study treatment and for 3 months after last dose of study drug(s) to prevent pregnancy in a partner. Acceptable methods of contraception to be used in this study include:

- **Condom with spermicide and** one of the following:
  - Oral contraceptive or hormonal therapy (e.g. hormone implants)
  - Placement of an intra-uterine device

- **Acceptable non-hormonal birth control methods include:**
  - Total sexual abstinence. Abstinence must be for the total duration of the study and the drug washout period.
  - Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
  - Tubal occlusion plus male condom with spermicide
  - Intrauterine Device (IUD) plus male condom+spermicide. Provided coils are copper-banded
- **Acceptable hormonal methods:**
  - Etonogestrel implants (eg, Implanon, Norplan) + male condom with spermicide
  - Normal and low dose combined oral pills + male condom with spermicide
  - Norelgestromin/ethinyl estradiol (EE) transdermal system + male condom with spermicide
  - Intravaginal device + male condom with spermicide (eg, EE and etonogestrel)
  - Cerazette (desogestrel) + male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

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

3.2 Exclusion Criteria:

3.2.1 Patients who have had chemotherapy, hormonal therapy (except LHRH agonist or antagonist), immunotherapy, radioisotope therapy, or RT within 21 days prior to start of the study agents.

3.2.2 Initiating bisphosphonate, or RANKL antibody therapy or adjusting the dose/regimen within 30 days prior to Cycle 1 Day 1 is prohibited. Patients on a stable bisphosphonate regimen are eligible and may continue.

3.2.3 Patients who have received any other investigational agents within the past 28 days prior to Cycle 1 Day 1.

3.2.4 Patients with untreated brain metastases, spinal cord compression, or evidence of symptomatic brain metastases or leptomeningeal disease as noted on computed tomography (CT) or magnetic resonance imaging (MRI) scans are excluded from this clinical trial, since neurologic dysfunction may confound the evaluation of neurologic and other AEs. While screening Brain MRI is not required, it should be performed if clinically indicated at the discretion of the treating investigator. Should patient found to have brain metastasis, treatment of brain metastasis must precede the participation in this study.

3.2.5 For patients with known and treated brain metastases is allowed in this study if they fulfill **ALL** of the following criteria:

- The lesions have remained radiologically stable for at least six weeks after completion of brain irradiation or stereotactic brain radiosurgery, and must remain stable at the time of study entry.
- There is no mass effect present radiologically and no steroids requirement for symptom control for more than 4 weeks.

3.2.6 Patients who have received a prior inhibitor of VEGF signaling inhibitor, or a PARP inhibitor administered.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cediranib or olaparib.

3.2.8 Concomitant use of known **strong CYP3A inhibitors** (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir), **moderate CYP3A inhibitors** (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil), **strong CYP3A inducers (**eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or **moderate CYP3A inducers** (eg. bosentan, efavirenz, modafinil) (See Appendix D for updated list from FDA website).

A minimum washout period of **2 weeks** prior to cycle 1 day 1 is required for **strong inhibitors,** and **at least one week** for **moderate inhibitors.** A minimum washout period of **4 weeks** prior to cycle 1 day 1 is required for **CYP3A inducers**. A minimum washout period of **5 weeks** prior to cycle 1 day 1 is required for **enzalutamide or phenobarbital**. Dihydropyridine calcium-channel blockers are permitted for management of hypertension.

3.2.9 Current use of natural herbal products or other "folk remedies." If using previously, patients must stop using natural herbal products while participating in this study. Multivitamin, Ca/Vit D and other vitamin complex supplements are allowed.

3.2.10 Patients with concomitant or prior invasive malignancies within the past 5 years. Subjects with limited stage basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the breast, or non-muscle invasive bladder cancer, are eligible as long as they received curative intent therapy.

3.2.11 Uncontrolled intercurrent illness including, but not limited to, uncontrolled seizures ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.12 Resting ECG with QTc > 470 msec on two or more time points within a 24 hour period, noted within 14 days of treatment, or family history of long QT syndrome.

3.2.13 History of myocardial infarction within 6 months of the randomization.

3.2.14 History of stroke or transient ischemic attack within 6 months of the randomization

3.2.15 NYHA classification of III or IV.

3.2.16 Current cardiac arrhythmic condition requiring concurrent use of anti-arrhythmic drug. Rate controlled atrial fibrillation is allows.

3.2.17 History of hypertensive crisis or hypertensive encephalopathy within 3 years of the randomization

3.2.18 Clinically significant peripheral vascular disease or known abdominal aortic aneurysm (>5cm in diameter) or history of aortic dissection. Patients with known history of AAA with $\geq$ 4cm in diameter, a repeat US within the last 6 months prior to randomization will be required to document that it is $\leq$ 5cm, and patient must be asymptomatic from the aneurysm, and the blood pressure must be well controlled as required in this protocol.

3.2.19 A major surgical procedure, open biopsy, or significant traumatic injury within 3 months prior to Cycle 1 Day 1 (percutaneous/endobronchial/endoscopic biopsies are allowed).

3.2.20 History of bowel obstruction within 1 month prior to starting study drugs.

3.2.21 History of hemoptysis within the last 1 month prior to randomization

3.2.22 Presence of cavitation of central pulmonary lesion, or radiographic evidence of pneumonitis or other extensive bilateral lung disease such as interstitial lung disease.

3.2.23 Any history of GI perforation, history of intra-abdominal abscess within 3 months prior to starting treatment, or history of abdominal fistula unless the fistula history meets all the following: (a) the fistula was surgically repaired, (b) there has been no evidence of fistula for at least 6 months prior to starting treatment, (c) patient is deemed to be at low risk of recurrent fistula, and (d) the case must be discussed with the study PI.

3.2.24 Current dependency on IV hydration or total parenteral nutrition (TPN).

3.2.25 Known coagulopathy or bleeding diathesis. Those on therapeutic anticoagulation or anti-platelet agent are permitted only after discussing with the study PI. See Section 5.2 for monitoring of anticoagulation therapy.

3.2.26 Patients with history of intra-abdominal bleeding or retroperitoneal bleeding within the last 3 years are excluded

3.2.27 Patients with myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML), or features suggestive of MDS/AML.

3.2.28 Patients with known active human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C infection. It is because of the potential requirement for anti-viral therapies that are prohibited on the study. Patients with a history of hepatitis B or hepatitis C, who are deemed cured and no longer require treatment may be allowed to enroll after consultation with the respective specialist and the Study PI.

3.2.29 Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)

3.2.30 Whole blood transfusions in the last 120 days prior to entry to the study.

3.2.31 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

3.2.32 Previous enrollment in the present study

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the

satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and

NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

4.2 Site Registration

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

If interested in participating in this study, an investigator or his/her team at the participating site must discuss with the Study PI via email: joseph.w.kim@yale.edu

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

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

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

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

The CTSU Regulatory Office tracks receipt of these documents in the CTSU Regulatory Support System (RSS), reviews for compliance, and transmits site approval data to CTEP.

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

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the NCI Protocol #9984 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-CT018, and protocol #9984.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Submitting Regulatory Documents

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

4.2.3 Requirements For Protocol #9984 Site Registration:

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

4.2.4 Checking **Site** Registration Status

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

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM

username and password

- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

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

4.2.5 Ordering Blood Pressure Cuffs

As a part of site initiation, each participating site must order blood pressure cuffs for their expected number of accrual:

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Protocol tab at the top of your screen.
- Click on the ETCTN subtab.
- Click on the following folders: Phase 1 Grants / LAO-CT018 / 9984 / LPO Documents / Miscellaneous
- Click Shipment Authorization Form for Blood Pressure Cuffs

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

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

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or

Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type. If 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/IWRS, site staff should verify the following:

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

4.3.3 OPEN/IWRS Questions?

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

4.4 General Guidelines

Following registration, patients should begin protocol treatment within **7** days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

Androgen deprivation therapy is a standard therapy for all patients with mCRPC. Patients in **both Arms A and B,** unless undergone bilateral orchiectomy, must continue with LHRH or GnRH agonists throughout the study as a standard of care. The therapy must have been initiated at least 4 weeks prior to Cycle 1, Day 1.

5.1 Agent Administration

The treatment assignment is done via randomization on a 1:1 basis to receive either cediranib and olaparib combination (Arm A) or olaparib monotherapy (Arm B) (See Section 4.3 for registration/randomization process). The study treatment is not blinded with regards to whether patients are receiving the combination therapy or olaparib monotherapy.

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

One cycle will be considered 28 days.

5.1.1 **Arm A:** Cediranib and Olaparib Combination

Olaparib **200mg (two 100mg tablets)** orally twice daily continuous dosing. Cediranib **30mg** in tablet formulation orally once daily.

Patients randomized to Arm A will be required to maintain medication and blood pressure diaries (See Appendix F). Patients will be instructed in its use, and asked to bring it with them to each appointment. Patients should avoid grapefruit juice while on study, due to P450 interactions with olaparib.

A blood pressure cuff will be provided to patients randomized to Arm A. See Section 4.2.5 for the site to order blood pressure cuffs. Patients on this arm must be counseled on the blood pressure monitoring and diarrhea management. It is **highly advisable that patients should have an anti-hypertensive and an anti-diarrheal prescribed prior to starting cediranib**. Please refer to Appendix G and Appendix H.

5.1.1.1 Cediranib

Cediranib at the appropriate dose level will be given orally continuously each morning on an empty stomach, either 1 hour before or 2 hours after breakfast. Patients should not "make up" a missed dose or a dose that was vomited. Patients should take cediranib with a glass of water. Cediranib may be taken at the same time as the morning olaparib dose.

5.1.1.2 Olaparib

Olaparib at the appropriate dose level will be given orally continuously twice daily, with doses taken at the same times each day approximately 12 hours apart. The correct number of, 100 mg, or 150 mg tablets comprising the appropriate dose should be taken at the same times each day with approximately 240 mL of water. The morning dose may be taken at the same time as the cediranib dosing. The evening dose may be taken with a light meal/snack. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken, and the patient should take their allotted dose at the next scheduled time.

5.1.2 **Arm B:** Olaparib monotherapy

Olaparib **300 mg (two 150mg tablets) orally twice daily** continuous dosing. Patients randomized to Arm B will be required to maintain a medication diary (See Appendix E).

Olaparib at the appropriate dose level will be given orally continuously twice daily, with doses taken at the same times each day approximately 12 hours apart. The correct number of, 100 mg, or 150 mg tablets comprising the appropriate dose should be taken at the same times each day with approximately 240 mL of water. The evening dose may be taken with

a light meal/snack. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken, and the patient should take their allotted dose at the next scheduled time.

5.2 General Concomitant Medication and Supportive Care Guidelines

Patient should receive general concomitant and supportive care medications based on best medical practice. All medications must be recorded in the case report form and be reviewed by the treating physician at each visit.

5.2.1 Prostate Cancer Related Supportive Therapies

- Luteinizing hormone-releasing hormone (LHRH) agonist or antagonist, to maintain a testosterone level <50g/dL should be administered in patients who have not undergone an orchiectomy as a standard of care.

- The patient can receive a stable dose of corticosteroids before and during the study as long as these were commenced at least 4 weeks prior to treatment. Higher doses of steroids are permitted if clinically indicated for acute medical conditions, such as prevention or treatment of contrast allergy.

- Initiating bisphosphonate, or RANKL antibody therapy or adjusting the dose/regimen within 30 days prior to Cycle 1 Day 1 is prohibited. Patients on a stable bisphosphonate or RANKL therapy regimen are allowed and may continue.

- Conventional multi-vitamins and minerals, such as Calcium and Vitamin D supplements are allowed on study.

5.2.2 **Medications that may NOT be administered:**

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (**except androgen deprivation therapy**), palliative radiotherapy (exception may be given), biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

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

Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of **herbal supplements,** or other **"folk remedies"** is **prohibited** during

the study (including, but not limited to, cannabis, St. John's wort, kava, ephedra [ma huang], ginkgo biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng).

5.2.3 Restricted concomitant medications (Olaparib IB Edition Number 14, 10 March 2017)

Appendix D provides a list of drugs that are prohibited. Appendix C-1 and Appendix C-2 (Patient Drug Information Handout and Wallet Card) should be provided to patients.

Strong or Moderate CYP3A inhibitors
Known **strong** CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or **moderate** CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) **MUST NOT** be taken with olaparib. Treating investigator **MUST** check with the FDA website cited in Appendix D for the updated list.

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

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100mg bd for the duration of concomitant therapy with the strong inhibitor and for 5 half lives afterwards.

- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150mg bd for the duration of concomitant therapy with the moderate inhibitor and for 3 half lives afterwards.

- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

Strong or Moderate CYP3A inducers
Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and **moderate** CYP3A inducers (eg. bosentan, efavirenz, modafinil) of CYP3A **MUST NOT** be taken with olaparib. Treating investigator **MUST** check with the FDA website cited in Appendix D for the updated list

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

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

P-gp inhibitors
It is possible that co-administration of P-gp inhibitors (eg amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

Effect of olaparib on other drugs

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

- Based on limited in vitro data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp.

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

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

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

5.2.4 Other supportive care guideline

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

For the research tumor biopsy, the anticoagulant therapy should be held prior to the scheduled biopsy at the discretion of the treating investigator in accordance with the institution's guideline.

Anti-emetics/Anti-diarrheal
If a patient develops nausea, vomiting and / or diarrhea, then these symptoms should be reported as AEs, and appropriate treatment of the event given.

Palliative radiotherapy
Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression or radiographic progression during the study period. Study treatment should be discontinued for **a minimum of 3 days before** a patient

undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered. This **must be** discussed with overall **Study PI.**

Administration of other anti-cancer agents
Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

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

5.3 Criteria for Taking a participant OFF protocol therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), or adverse event(s) requiring study medication(s) to be discontinued (See Important Safety Information of the section 6.1)
- Patient decides to withdraw from treatment or the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient’s non-compliance that render further treatment unacceptable in the judgment of the investigator

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

5.4 Duration of Follow Up

Patients who discontinue therapy due to reasons other than radiographic disease progression, will be followed until radiographic disease progression or initiation of the subsequent therapy is documented.

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

All participants’ vital status may be followed after removal from the study treatment via a phone

call or medical records review every 6 months and using publicly available databases.

5.5 Criteria to take a participant OFF study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

5.6 Criteria for cross-over to cediranib/olaparib combination arm.

For patients in Olaparib monotherapy arm will have an option to cross over to the combination upon documented radiographic progression as defined in the primary objective (Section 1.1), not by PSA progression.

Before receiving the combination therapy, patient must meet all the Patient Section criteria in Section 3: except the following:

- No washout is required from the last dose of olaparib therapy.
- The biopsies before cross-over treatment and at on-treatment are highly encouraged if they have easily accessible tumor but not required. On-treatment biopsy may be done during the 4th week of the combination therapy.
- Angiome panel blood draw will be required.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Arm A: Management of Cediranib and Olaparib Related Adverse Events

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.

Table 1: Dose Modification of Cediranib

Dose level	**Cediranib**
1 (starting dose)	30 mg (two 15mg tablets) orally, once a day
-1	20 mg (one 20mg tablet) orally, once a day
-2	15 mg (one 15mg tablet) orally, once a day

Table 2: Dose Modification of Olaparib

Dose level	Olaparib Tablet
1 (starting dose)	200 mg (two 100mg tablets) orally, every 12 hours
-1	150mg (one 150mg tablet) orally, every 12 hours
-2	100 mg (one 100mg tablet) orally, every 12 hours

IMPORTANT SAFETY INFORMATION

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 3 weeks. Once dose of study drug(s) have been reduced, no dose re-escalation is permitted.

If treatment has to discontinue due to toxicity, both IPs (cediranib and olaparib) should be discontinued at the same time; patients are not allowed to remain in the study if they are taking either cediranib or olaparib as monotherapy. However, in rare circumstances, patients experiencing ongoing clinical benefit but who develop one of the toxicities listed below related to one of the IPs that prevents them to continue to take this IP, may be allowed to continue on the unrelated drug if in the opinion of the treating investigator the risk benefit remains favorable and only after discussion with the Principal Investigator.

AEs requiring **cediranib** to be discontinued:

- GI perforation
- Arterial Thromboembolic Event
- PRES
- Severe hemorrhage
- Severe persistent hypertension despite maximal anti-hypertensive treatment

AEs requiring **olaparib** to be discontinued:

- Bone marrow findings consistent with MDS/ AML
- Severe persistent anemia
- Pneumonitis

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 Principal Investigator, 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 Principal Investigator.

6.1.1 Hematologic Toxicity

6.1.1.1 Management of neutropenia and thrombocytopenia

Neutropenia and thrombocytopenia are recognized common adverse drug reactions reported for both olaparib and cediranib. Treatment should be managed according to Table 3:

	Olaparib dose	**Cediranib Dose**
CTCAE Grade 1-2 ANC >1.0 G/L or Platelet count >50 G/L	Investigator judgement to continue treatment or allow dose interruption; dose interruptions should be for a maximum of 3 weeks; appropriate supportive treatment and causality investigation	Investigator judgement to continue treatment or allow dose interruption; dose interruptions should be for a maximum of 3 weeks; appropriate supportive treatment and causality investigation
CTCAE grade 3-4 ANC <1.0 G/L or Platelet count <50 G/L	Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 3 weeks. Upon recovery, olaparib dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one or both IPs	Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 3 weeks. Upon recovery, cediranib dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one or both IPs

Abbreviations: ANC absolute neutrophil count; CTCAE common terminology criteria for adverse events; IP investigational product

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. Prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) highlight that there is a potential risk of shortening the time to tumor progression or disease-free survival. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. The package inserts should be consulted.

Febrile Neutropenia
If a patient develops febrile neutropenia, both cediranib and olaparib should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours of the last dose of olaparib unless absolutely necessary.

When ANC is >1.5x10^9/L and patient remains afebrile for >72 hours, the study drug (s) can be restarted at one dose level lower than the prior. Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

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

Dose modifications for hematologic toxicity

Patients who have IPs held for hematologic toxicities should have blood counts and differentials checked ***at least weekly until recovery***; these data should be recorded in eCRF as extra laboratory examinations. If counts do not improve to CTCAE Grade 1 or better despite drug cessation for 3 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 drug, study drug may be withheld for up to 3 weeks at the discretion of the treating Investigator.

6.1.1.2 Management of anemia

Anemia is a common adverse drug reaction related to olaparib. Cediranib is not reported to increase the risk of anemia. Management of anemia is in accordance with Table 4:

Table 4: Management of anemia

	Olaparib dose	**Cediranib dose**
Hb <10 but ≥8 g/dL	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib or interrupt dose for a maximum of 3 weeks. If repeat Hb <10 but ≥8 g/dL, dose interrupt until Hb ≥10 g/dL for maximum of 3 weeks and upon recovery dose reduce to 150 mg bd as a first step and to 100 mg bd as a second step.	No change
Hb < 8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt olaparib until **improved** to Hb ≥10g/dL. Upon recovery dose reduce to **150mg bd**	No change

Abbreviations: bd twice daily; Hb hemoglobin

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and

hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. Any subsequently required dose interruptions, related to development of anemia, or coexistent with newly developed neutropenia, and/or thrombocytopenia, will require olaparib dose reductions to 150 mg twice daily as a first step and to 100 mg twice daily as a second step.

If Hb drops to < 8 g/dL despite the dose reduction or more than one blood transfusion is required to recover Hb levels with no alternative explanation for the anemia, olaparib should be permanently discontinued.

6.1.1.3 **Management of prolonged hematological toxicities while on study treatment**

If a patient develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in olaparib due to CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in 1 or both IPs due to CTCAE Grade ≥3 neutropenia (ANC <1 x 10^9/L)
- ≥2 week interruption/delay in 1 or both IPs due to CTCAE Grade ≥3 thrombocytopenia and/or development of platelet transfusion dependence (Platelets <50 x 10^9/L)

Check **weekly differential blood counts including reticulocytes and peripheral blood smear**. If any blood parameters remain clinically abnormal after 3 weeks of dose interruption, the patient should **be referred to hematologist for further investigations**. **Bone marrow analysis and/or blood cytogenetic analysis should be considered** at this stage according to standard hematological practice. Both IPs should be discontinued if blood counts do not recover to CTCAE Grade ≤1 within 3 weeks of dose interruption.

Bone marrow or blood cytogenetic analysis may be performed according to standard hematological practice for patients with prolonged hematological toxicities as defined 6.1.1.3 above. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to CTEP. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.

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

6.1.2 **General Management of Non-Hematologic Adverse Events**

Cediranib should be discontinued should any of the following AEs occur: GI perforation; arterial thromboembolic events; PRES (radiologically confirmed); severe or medically significant hemorrhage and severe persistent hypertension despite maximal anti-hypertensive treatment.

Dose modifications for other non-hematologic events on IPs should be managed according to **Table 5 below.**

Table 5: General Management of Adverse Events (Non-Hematologic)

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
Any grade 2 non-hematologic AE (excluding hypertension or other AEs with specific management instructions outlined in the sections below, or easily correctable asymptomatic grade 2 laboratory abnormalities) related to cediranib or olaparib that resolve **within 72 hours with or without supportive care.**	Hold study drug(s) for up to 21 days until toxicity resolves to ≤ 1 grade 1. Treatment may be **restarted at the same dose without dose reduction if the nature of these toxicities are tachyphylaxes (e.g., headache or nausea)** We expect toxicities, such as grade 2 headache, and grade 2 nausea, to diminish or improve to grade 1 or less, by holding the drug(s) with or without supportive care, within 3 days. If so, the treatment may be restarted at the same dose without dose reduction at the discretion of the treating physician. If, however, the AEs recur at grade 2 again upon restart, then it would require dose-reduction of the suspected drug(s). If the initial grade 2 AE does not improve to grade 1 or less within 3 days, then the drug-hold will continue until the AE improves to grade1 or less. As long as it recovers within 14 days, the drug(s) can be resumed, but at a reduced dose level.
Any grade 2 non-hematologic AE (excluding hypertension or other AEs with specific management instructions outlined in the sections below, or easily correctable asymptomatic grade 2 laboratory abnormalities) related to cediranib or olaparib **that persists despite maximal support.**	Hold study drug(s)[1] for up to 21 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 6.1 (for Arm A) and section

	6.2 (for Arm B), at the treating investigator's discretion.[2] The overall PI of the study should be informed regarding all dose modifications. Patients whose toxicity has not resolved after 21days will be removed from study. Patients experiencing persistent Grade 2 fatigue that is felt to be acceptable by both patient and treating investigator may continue on study drug without dose hold or reduction at the treating investigator's discretion.
Any grade 3 non-hematologic (excluding grade 3 hypertension or easily correctable asymptomatic grade 3 laboratory abnormalities)	Hold study drug(s)[1] for up to 21 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 6.1 (for Arm A) and section 6.2 (for Arm B) at the treating investigator's discretion.[2] The study PI of the study should be informed regarding all dose modifications.
Grade 3 non-hematologic AE (excluding grade 3 hypertension or easily correctable asymptomatic grade 3 laboratory abnormalities) related to cediranib and olaparib combination that does **not resolve to grade 2 or less within 21 days** despite maximum supportive care and treatment hold.[3] **Grade 3** myocardial infarction or acute coronary syndrome	Unless specified elsewhere, discontinue study drug(s) causing the toxicity permanently.
Grade 4 non-hematologic AE (excluding easily correctable asymptomatic grade 4 laboratory abnormalities), related to cediranib or olaparib or both.	Unless specified elsewhere, discontinue study drug(s) causing the toxicity permanently.
[1]At the discretion of the investigator, the study drugs may be held or dose modified independently if the observed toxicity is attributed to only one of the drugs, while the patient continued to receive the drug not associated with the observed toxicity. The time a given drug is held should not exceed 14 days. For **grade 3 fatigue, both** cediranib and olaparib should be held and then dose-reduced. [2] If a patient has a grade 3 or higher toxicity at the lowest dose level (excluding grade 3 hypertension or easily correctable asymptomatic grade 3 laboratory abnormalities), the	

suspected drug must be discontinued.

[3]Excluding hypertension, **for venous thromboembolic events, treatment may be resumed at the discretion of the investigator after discussing with the Study PI, once patient is asymptomatic.**

6.1.3 Management of cediranib-related toxicities

6.1.3.1 Hypertension (See APPENDIX G for suggested oral anti-hypertensives)

Increases in BP and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following cediranib treatment has been seen in animal studies as well as clinical trials.

Only doses of cediranib will be modified for hypertension; olaparib doses will not be reduced unless other toxicities are experienced. Patients receiving cediranib should be provided with blood pressure monitors for home use and will check and record their blood pressures at least twice daily while on study treatment. When BP is stable for at least 8 weeks, then BP monitoring can be reduced to once daily. Should further hypertension arise, return to twice daily monitoring, until at least 8 weeks of stability then can return to daily.

See the tables below for hypertension management and suggested antihypertensive medications by class.

Note:

- If patients require a delay of >1 week for management of hypertension, management should be discussed with the study PI.
- If patients require a delay of >3 weeks for management of hypertension, discontinuation of cediranib may be considered after discussing with the Study PI.
- 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 v5.0. Please note: patients may have baseline hypertension meeting CTCAE grading criteria on study entry provided this is adequately controlled on maximum of 3 antihypertensive medications. Patients with baseline hypertension who require the addition of new medications for hypertension management while on study drug may not have an increase in CTCAE grade, but a change in attribution should be noted.
- While patients are receiving treatment with cediranib, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 AE.
- Stopping or reducing the dose of cediranib is expected to cause a decrease in BP. Continue to monitor BP twice daily and decrease the monitoring to once a day once stability is achieved. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly.

Table 6.3: Hypertension Monitoring and Management

• See Appendix G 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)

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 hypertension-related complications	Standard monitoring per treating MD	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. Escalate dose of medication in stepwise fashion until BP is controlled or at a maximum dose If BP is not controlled to < 140/90 mmHg with one drug regimen, then add a second agent. **Study drug does not need to be held**	Increase frequency of monitoring until stabilized **to BP <140/90 mmHg.**	Do not hold cediranib unless otherwise clinically necessary

		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 two drug combinations. Additional antihypertensive drugs, up to a total of 4, may be maximized for blood pressure control.** Consider consult with a BP 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 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 drug (up to 14 days) until maximum effect of the antihypertensive agents is achieved. If BP is reduced to less than 140/90 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 antihypertensive agents.	Intensive BP monitoring (hospitalization if necessary)	**Hold cediranib for up to 21 days and repeat BP.** If BP is reduced to less than 140/90 within 7 days, cediranib may be resumed at a reduced dose after discussion with the Study PI and/or sponsor.

6.1.3.2 Proteinuria

Proteinuria has been observed in cediranib studies. Patients with a urine protein to creatinine ratio (UPC) of greater than 1.0 at entry are ineligible. Increases in proteinuria may occur during treatment and should be managed as follows:

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 21 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 Section 6.1.2 and 6.1.3.14. .		

6.1.3.3 Decrease in LVEF

Patients who have any of the following should undergo an echocardiogram (ECHO) **at baseline** and **every 4 cycles** while on cediranib/olaparib therapy and when clinically indicated:

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- Prior central thoracic RT, including RT to the heart
- History of myocardial infarction within 6 to 12 months or history of other significant impaired cardiac function (Patients with history of myocardial infarction within 6 months are excluded from the study)

The decision to continue or interrupt cediranib/olaparib is based on the LVEF as it relates to the institution's LLN and change in ejection fraction from screening (LVEF as measured at enrollment) according to Table below.

Relationship of LVEF to Institution's LLN at baseline	LVEF Decrease <10%	LVEF Decrease 10-15%	LVEF Decrease >15%
LVEF Normal	Continue cediranib	Continue and repeat ECHO within 4-8 weeks	Continue and repeat ECHO within 4-8 weeks
1-5% below LLN	Continue and repeat ECHO within 4-8 weeks	**Interrupt cediranib and repeat ECHO within 3 weeks. Initiate Cardiology**	**Interrupt cediranib and repeat ECHO within 3 weeks Initiate Cardiology**

		Consult	**Consult**
≥6% below LLN	Continue and repeat ECHO within 4-8 weeks	**Interrupt cediranib and repeat ECHO within 3 weeks Initiate Cardiology Consult**	**Interrupt cediranib and repeat ECHO within 3 weeks Initiate Cardiology Consult**

Abbreviations: ECHO echocardiogram; LLN lower limit of normal; LVEF left ventricular ejection fraction; MUGA multigated acquisition. LVEF decreases in percentage points.

The treating investigator may resume cediranib at one dose level lower than the prior **after discussing with the study PI** when all the following are met:

- The repeat Echo shows LVEF≥LLN, or LVEF is recovered back to baseline within **4 weeks.**
- Patient must be free of clinical signs and symptoms of heart failure.

Unless recovered within 4 weeks (i.e, cediranib held for >4 weeks), stop cediranib permanently.

6.1.3.4 Diarrhea

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

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 16 mg in a 24-hour period. Patients should be also be counseled to start BRAT diet (Banana, Rice, Applesauce, and Toast).
	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.

	Patients should be instructed to contact their study physician if mild or moderate (NCI CTCAE Grade 1 or 2) diarrhea persists for over 48 hours despite treatment with loperamide and cediranib dose interruption.
Persistent grade 2 diarrhea for >7 days of holding cediranib, or Initial grade 3 or 4 diarrhea	Hold **both** cediranib and olaparib for **up to 14 days** until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower, as per the dose reduction levels in Section 6.1
Grade 3 or 4 diarrhea lasting **>14 days** despite maximum supportive care and treatment being held	Discontinue study drugs permanently.
Recurrent grade 3 or 4 diarrhea	Hold both cediranib and olaparib for up to 7 days until toxicity resolves to ≤ grade 1. If the diarrhea last >7 days despite maximal supportive care and treatment being held, discontinue study drugs permanently.

6.1.3.5 Management of Thyroid Toxicities

The use of cediranib has been associated with elevations of TSH and patients should be managed as per the following schema and chart:

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.

In all of the above cases, study treatment should continue unless clinically contraindicated. Referral to an endocrinologist should also be considered if thyroid abnormalities occur. Patients already on thyroid replacement hormone who require adjustment of their replacement regimen will be considered to have a drug-related toxicity.

6.1.3.6 Gastrointestinal Perforation

Gastrointestinal perforation, sometimes associated with fistula formation, has been observed in

patients receiving cediranib. Some events of gastrointestinal perforation have been fatal but causality could not be unequivocally assigned to cediranib.

Cediranib should be permanently discontinued in those patients who experienced gastrointestinal perforation or fistula. All events of gastrointestinal perforation are followed up and an assessment should be made on their relationship to the underlying tumor.

6.1.3.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of MRI-documented posterior reversible encephalopathy syndrome (PRES), including RPLS, have been reported in patients receiving cediranib in clinical studies. Cediranib should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure, if hypertension is present. Cediranib should be discontinued upon diagnosis of RPLS. After consultation with the PI and the NCI, consideration of restarting the study may be evaluated in light of any clinical benefit.

6.1.3.8 Fatigue

Fatigue is a common adverse drug reaction reported for both **cediranib and olaparib**. Fatigue experienced by patients taking cediranib may be rapid in onset. During clinic visits, patients fatigue levels should be discussed. Patients should seek medical advice early if Grade 2 fatigue develops (moderate fatigue causing difficulty performing some activities of daily living).

Care should be taken to ensure that the nutritional status of the patients is optimized and patients should be encouraged to drink plenty of fluids. Patients should be encouraged to manage fatigue by alternating periods of rest with light aerobic exercise, which may improve the symptoms in some cases.

Consideration should be given to other possible causes of fatigue (e.g., thyroid function, depression/insomnia and other concomitant medicinal products). Additionally, short interruption of cediranib dosing (initially 2-3 days-or longer-up to a maximum of 21 days) may help relieve fatigue. When symptoms improve cediranib should be restarted with the same dose or, if necessary, a dose reduction can be considered.

When Grade 3 or 4 fatigue develops, **both cediranib and olaparib** should be held for a maximum of 3 weeks or until it improves to grade 1 or baseline. Upon improvement, both drugs should be dose-reduced.

6.1.3.9 Fistula

In patients treated with cediranib, fistula has been reported and reflected the location of the underling malignancy. In the ovarian cancer population, vaginal fistula has been uncommonly reported in cediranib treated patients. Cediranib should be used with caution in patients at risk of fistula and discontinuation of cediranib should be considered in patients who develop fistulae.

6.1.3.10 Arterial thromboembolism

Arterial thromboembolic events (including transient ischemic attack and ischemic stroke) have been reported in clinical studies with cediranib. Cediranib should be used with caution in patients who are at an increased risk of thrombotic events or who have a history of thrombotic events. Cediranib should be permanently discontinued in patients who develop an arterial thromboembolic event.

6.1.3.11 Venous thromboembolism

Venous thromboembolic events including pulmonary embolism and deep vein thrombosis have been commonly reported in patients treated with cediranib. Anticoagulant treatment should be started in accordance with clinical practice. Discontinuation of cediranib **may** be considered. Cediranib should be used with caution in patients at risk of venous thromboembolism.

6.1.3.12 Wound healing

Treatment with cediranib should be stopped at least 2 weeks prior to scheduled surgery. The decision to resume cediranib therapy after surgery should be based on clinical judgment of adequate wound healing. In patients who experience wound healing complications during therapy, treatment with cediranib should be interrupted until the wound is fully healed. No formal studies of the effect of cediranib on wound healing have been conducted; however in the ICON6 pivotal study there was no evidence of an increase in wound healing complications in cediranib treated patients compared with placebo.

6.1.3.13 Elderly

There is a limited amount of safety data available for cediranib use in patients aged 75 years and older. Based on a population PK analysis, the clearance of cediranib decreased with age, however, no dose adjustment is needed given the small impact on exposure or variability. Caution should be taken when treating patients who are aged 75 years or older with cediranib. In case of toxicity dose pause or dose reduction may be considered.

6.1.3.14 Mild/moderate renally impaired patients

Patients with mild and moderate renal impairment discontinued cediranib more often due to adverse events, particularly when cediranib was co-administered with chemotherapy. Population PK analysis showed that no adjustment of cediranib dose is required in this population as cediranib is minimally renally cleared; however, cediranib clearance may be decreased in patients with low body weight. In the ICON6 pivotal study, patients with mild or moderate impairment had lower median body weight compared with patients with normal renal function. Caution should be exercised in patients with mild and moderate renal impairment and a cediranib dose adjustment should be considered in case of signs of toxicity.

For information on use of olaparib in renally-impaired patients, please see Section 6.1.4.5

6.1.3.15 Weight decreased

In the ICON6 study, weight decreased was very commonly reported in cediranib treated patients. Weight loss (≥7%) in cediranib-treated patients was associated with higher incidence of decreased appetite, vomiting and stomatitis, although these events were also commonly reported in patients who did not lose weight.

6.1.3.16 Rotator Cuff injury

A limited number of patients have experienced rotator cuff injuries while receiving the combination of cediranib and olaparib. Patients should therefore be monitored closely for the development of any shoulder pain or weakness.

Management of Rotator Cuff Symptoms			
Grade	Symptoms/Findings	Action	Dose modifications
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Limit heavy lifting or carrying of heavy objects, bags or backpacks. Consider shoulder MRI if symptoms warrant.	None.
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Obtain shoulder MRI if not previously obtained. If rotator cuff injury present on MRI, refer for physical therapy. Consider referral to orthopedics for evaluation as appropriate.	Hold cediranib and olaparib for up to 14 days until symptoms resolve to Grade 1 or less. Cediranib and olaparib may then be resumed at a reduced dose level of each study drug. If patient is on the lowest dose level(s) of cediranib or olaparib, please contact the study PI to discuss dose modifications.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Obtain shoulder MRI if not previously obtained. Refer to orthopedic surgeon for evaluation.	Hold cediranib and olaparib for up to 14 days until symptoms resolve to Grade 1 or less. Cediranib and olaparib may then be resumed at a reduced dose level of each study drug after discussion with the overall PI.

6.1.4 **Management of olaparib associated toxicity**

6.1.4.1 Management of MDS/AML

Patients who develop MDS/AML on treatment should be discontinued from olaparib treatment and managed appropriately.

6.1.4.2 Management of olaparib-related new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in 1 or both IPs dosing is recommended and further diagnostic workup (including a HRCT scan) should be performed to exclude pneumonitis.

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

6.1.4.3 Febrile Neutropenia

See 6.1.1.1 Management of Neutropenia and Thrombocytopenia

6.1.4.4 Management of Nausea and Vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. These events are generally 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 treatment with the IPs, 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. Taking olaparib tablets with food may help alleviate symptoms of nausea and vomiting.

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

6.1.4.5 Management of renal impairment

If subsequent to study entry and while still on study treatments, a patient's estimated creatinine clearance (CrCL) falls below the threshold for study inclusion (<50 mL/min), retesting should be performed promptly. A dose reduction of olaparib is recommended for patients who develop moderate renal impairment (calculated CrCL by Cockcroft-Gault equation of ≥31 mL/min and ≤50 mL/min) for any reason during the course of the study: the dose of olaparib should be reduced to 150 mg bd.

Because the CrCL determination is only an estimate of renal function, in instances where the CrCL falls to between 31 mL/minutes and 50 mL/minutes, the Investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (CrCL ≤30 mL/minutes) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued. For information on use of cediranib in renally-impaired patients, please see Section 6.1.3.14.

6.2 Arm B: Olaparib Monotherapy

Dose Modification Table

Dose Level	Olaparib Tablet
1 (starting dose)	300 mg (two 150mg tablets) orally, every 12 hours
-1	250 mg (one 150mg tablet and one 100mg tablet) orally, every 12 hours
-2	200 mg (two 100mg tablets) orally, every 12 hours

IMPORTANT SAFETY INFORMATION:
AEs requiring **olaparib** to be discontinued:

- Bone marrow findings consistent with MDS/ AML
- Severe persistent anemia
- Pneumonitis

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 Principal Investigator, 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 Principal Investigator.

6.2.1 Management of Hematological Toxicity

6.2.1.1 Management of Anemia

Table 6.2.1.1 Management of Anemia (Olaparib monotherapy Arm)

Hemoglobin	**Action to be taken**
Hb < 10 *but* ≥ 8 g/dl (CTCAE Grade 2)	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. If repeat Hb**< 10 *but* ≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step may be considered.
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks. until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 6.1.1.3 for the management of this.

6.2.1.2 Management of Neutropenia, leukopenia and thrombocytopenia

Table 6.2.1.2: Management of Neutropenia, leukopenia and thrombocytopenia (Olaparib monotherapy Arm)

Toxicity	**Study treatment dose adjustment**
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation

Toxicity	Study treatment dose adjustment
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

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

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops **febrile neutropenia,** study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

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

For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section 6.1.1.3.

6.2.1.3 Management of prolonged hematological toxicities while on study treatment

See the section 6.1.1.3

6.2.2 **General** Management of **Non-Hematological** Toxicities

See section 6.1.2 Table 5

6.2.3 Management of olaparib-associated toxicity

See the Section 6.1.4 the management of olaparib associated toxicity and its subsections

6.3 Interruptions for intercurrent non-toxicity related events

6.3.1 Arm A: Cediranib + Olaparib Arm

Cediranib and olaparib dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart the investigational products (IPs) within 3 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the study PI.

Both cediranib and olaparib should be stopped at least 2 weeks prior to planned surgery. After

surgery both IPs can be restarted when the wound has healed. **No stoppage of IPs is required for any needle biopsy procedure.**

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

6.3.2 ARM B: olaparib monotherapy arm

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

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

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

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

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

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

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

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

7.1.1 CAEPRs for CTEP IND Agents

7.1.1.1 CAEPR for cediranib

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)***

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%)**	
	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		
	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			

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%)**	
	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.

7.1.1.2 CAEPR for olaparib

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

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/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 2.5, July 1, 2021[1]

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

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%)**	
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			
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	

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

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

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

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

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

7.2 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

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

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

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating

physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

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

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

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

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

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

7.5 Secondary Malignancy

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

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

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

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

7.6 Second Malignancy

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

7.7 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or ***patient's partner*** from the time of consent to **90 days after the last dose of study drug** must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.8 Pregnancy loss

- Pregnancy loss is defined in CTCAE as "Death in utero."
- Any Pregnancy loss should be reported **expeditiously,** as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
- **A** Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS recognizes this event as a patient death.

7.9 Neonatal death

A neonatal death should be reported **expeditiously** as Grade 4, "Death neonatal" under the General disorders and administration SOC.

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agent(s)

No starter supplies will be provided. Study agents must be ordered after the patient is enrolled on the assigned treatment arm. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application.

8.1.1 Cediranib (AZD2171) (NSC 732208)

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

Other Names: cediranib, AZD2171 maleate

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

Molecular Formula: $C_{25}H_{27}FN_4O_3 \cdot C_4H_4O_4$ **M W:** 566.59 (maleate salt), 450.52 (free base)

Approximate Solubility: The aqueous solubility of AZD2171 (cediranib) is 0.0006 mg/mL for the free base (distilled water, pH 8.1 at 25°C) and 1.76 mg/mL for the maleate salt (distilled water, at 25°C).

Mode of Action: AZD2171 (cediranib) is a highly potent tyrosine kinase inhibitor of all three vascular endothelial growth factor receptors (VEGFR-1, -2 and -3). Inhibition of VEGF signaling leads to inhibition of angiogenesis, neovascular survival and vascular permeability. Pre-clinical tumor models show that AZD2171 (cediranib) reduces micro-vessel density and metastasis, indicating that it limits tumor growth.

How Supplied: Astra-Zeneca supplies and CTEP, NCI, DCTD distributes AZD2171 (cediranib). The agent is available as beige, round, biconvex, film-coated tablets containing 15 mg, and 20 mg of AZD2171 (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.

Storage: Store intact bottles at controlled room temperature below 30°C (86°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.

Route and Method of Administration: Oral. AZD2171 (cediranib) tablets should be taken either one hour before or two hours after meals.

Potential Drug Interactions: 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 show that AZD2171 (cediranib) 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.

In vitro studies show that AZD2171 (cediranib) is a weak inhibitor of BCRP, but not Pgp. Use caution in patients who are taking concomitant medications that are sensitive substrates of BCRP transporters since there is a potential for drug-drug interactions.

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.

Patient Care Implications: Agents that inhibit VEGF signaling have the potential to affect wound healing. For patients already enrolled onto the protocol, the manufacturer recommends holding AZD2171 (cediranib) for 2 weeks prior to elective surgery and restarting when the surgical wound is healed. Protocol exclusion criteria should include patients who have had major thoracic or abdominal surgery within 2 weeks prior to start of study or patients with any surgical incision that is not fully healed.

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

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

8.1.2 Olaparib (AZD2281) (NSC 747856)

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

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

Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

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

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

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

Description: crystalline solid

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

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

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

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

Storage: Store in a secure location below 30° C (86° F). 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 (AZD2281) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Route and Method of Administration: Tablets are taken by mouth and can be taken with a light meal/snack if needed to reduce stomach irritation. Olaparib tablets must be swallowed whole. Do not chew, dissolve, or crush the tablets.

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

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

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

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

Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should agree to use two (2) highly effective forms of contraception throughout study participation and for at least one (1) month after the last dose of olaparib. 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.

Availability: Olaparib is an investigational agent 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 Section 12.3)

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 Agent Ordering - NCI-supplied agents (AZD2171 (cediranib) and olaparib (AZD2281)) may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the -establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

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

8.1.3.3 Investigator Brochure Availability

The current versions of the IBs for 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 via email.

8.1.3.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm

- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- PMB IB Coordinator: IBcoordinator@mail.nih.gov

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

This is a randomized phase II prospective, multicenter study of olaparib and cediranib versus olaparib in men with metastatic castration resistant prostate cancer (mCRPC). This study incorporates several tissue-based and blood-based correlative studies to address the following objectives:

- To evaluate association of homologous recombination DNA repair deficiency (HRD) with the clinical activity of the combination of cediranib and olaparib or olaparib monotherapy, as measured by rPFS, in mCRPC patients. (integrated)

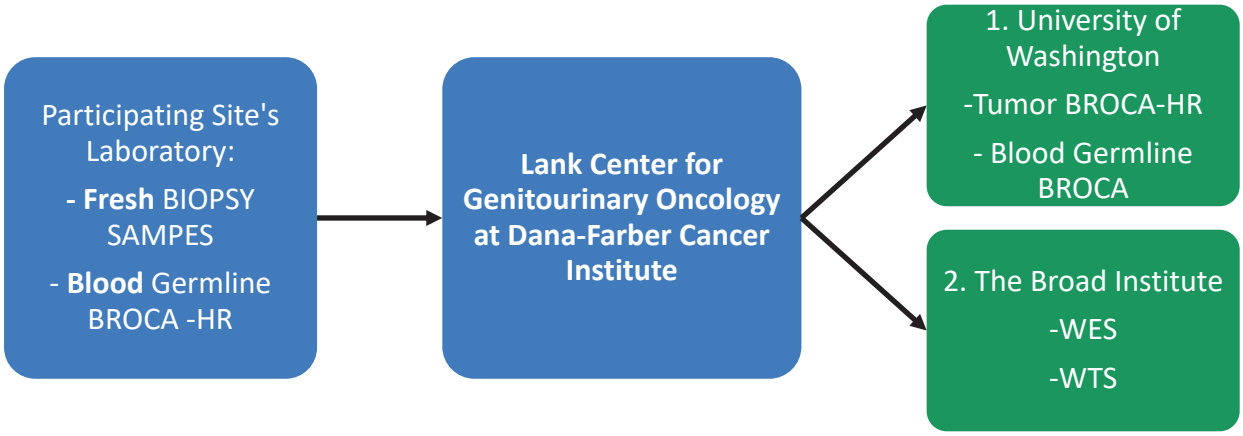
- To characterize genomic alterations by whole exome sequencing in mCRPC patients and correlate that with clinical activity or resistance to olaparib with or without cediranib. (integrated)

- To characterize changes in RNA expression of DNA repair genes, angiogenesis markers, and immune markers, by whole transcriptome sequencing and correlate with clinical activity or resistance to olaparib with or without cediranib (integrated).

- To identify baseline predictive biomarkers for rPFS or response and to identify on-treatment markers of acquired resistance in men with mCRPC receiving either olaparib plus cediranib or olaparib alone (exploratory).

- To explore biomarker signatures that correlate with the clinical activity or resistance to olaparib with or with cediranib, including changes in gene expression or acquired mutations in tumor biopsies (exploratory).

As shown in the flow diagram below, all the samples except plasma angiome panel, will be sent to the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute, as a central pathology processing for distribution of the biopsy tissue samples to appropriate destination.



The tumor tissue collections will occur via an image-guided (CT scan or US-guided) needle biopsy of a soft tissue or bone lesion. Biopsy of soft tissue is preferred when possible. Platelet count and coagulation profile will be checked prior to the biopsy as per institutional standard procedures. Heparin, low molecular weight heparin, aspirin, and other anti-platelet agents should be discontinued as per institutional standard procedures.

The baseline biopsy will be performed after registration/randomization, and within a maximum of 1 week, prior to the start of the protocol therapy (i.e., cycle 1 day 1). The protocol therapy should begin within 7 days after the biopsy unless any concern by the treating investigator, in which case, it must be discussed with the overall Study PI, prior to starting the therapy.

On-treatment biopsy will be done during the 4th week of the protocol therapy. While no stoppage of the study drug(s) is required for any needle biopsy, if any safety concern based on clinical factors the study drugs may be held pre and post biopsy, at the discretion of the treating investigator after discussing with the overall Study PI.

Post-progression biopsy is optional. Patients progressing on cediranib/olaparib or olaparib monotherapy may undergo a progression biopsy within 4 weeks from the last dose of the study treatment or prior to the starting the subsequent therapy, whichever comes first.

NOTE: If feasible, the on-treatment biopsy and progression biopsy should be taken from the same tumor lesion as the baseline biopsy.

Soft Tissue Biopsies:

Soft tissue biopsies will be performed per institutional standards and/or operator preference. Preferred soft tissue biopsy sites include: lymph nodes, peripheral based liver lesions, exophytic soft tissue components associated with bone lesions, subcutaneous nodules, pleural-based lesions, and kidney lesions. An 18 gauge or larger is preferred for soft tissue biopsies. Cautionary Note: liver biopsy is allowed. Caution should be taken given the risk of post-procedural hemorrhage.

Bone Biopsies:
Bone biopsies will be performed per institutional standards and/or operator preference. Bone biopsies should not be performed on irradiated lesions. Preferred bone sites include the lumbar vertebrae, pelvic bones and long bones. Use of the OnControl® Biopsy System is preferred when safe and appropriate (pelvic bones). Given lower yield on bone biopsy special attention should be given to the following parameters which may correlate with tumor yield on bone biopsy:

- Size
- Degree of sclerosis
- Distance from the skin to the lesion
- Distance from the cortex to the lesion
- Presence of a bone scan correlate
- Area to target for biopsy (center versus periphery of the lesion)

Important:
For each tissue collection procedure, the intent is to acquire **up to 6 needle cores** for rapid freezing in OCT medium. Size of these biopsy cores can be variable (0.1-1.0 cm). While larger cores are preferable to optimize tumor capture, cores of any size should be processed. Long cores approximately > 2 cm can be split. **A minimum of 3 cores is preferred.** If feasible, the on-treatment biopsy and an optional progression biopsy should be taken from the same tumor lesion as the baseline biopsy.

Refer to the Lab Manual for details of collection/processing of specimen/ shipping Information from Lank Center for Genitourinary Oncology at DFCI to the final destination (Appendices, I, J, K. and L)

Specimen Requirement:

Correlative Studies	Required Specimen	Collection Time Points
BROCA-HR (integrated)	Tumor biopsy specimen	Pre-treatment
	Whole blood (germline)	Pre-treatment
Whole Exome Sequencing (integrated)	Tumor biopsy specimen	Pre-treatment On-treatment Optional Post-progression
Whole	Tumor biopsy specimen	Pre-treatment

Transcriptome Sequencing (integrated)		On-treatment Optional Post-progression
Plasma Angiome Panel (integrated)	one 10ml lavender top (K2EDTA) tube of blood	Pre-treatment Day 1 of each cycle.

9.1 Integrated Correlative Studies

9.1.1 BROCA-HR – Integrated Laboratory Correlative Study

9.1.1.1 Collection of Specimen(s)

Refer to the Specimen Requirement Table above and Appendices I, J and L.

9.1.1.2 Handling of Specimens(s)

DNA will be extracted from PBMCs and FFPE tumor tissue 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 75 genes (BROCA-HR) that serve as a single assay for germline and somatic mutations that influence response to therapy will be utilized. Library preparation has been fully automated to increase sample turnaround and lower cost. Paired-end libraries with 350bp inserts will be prepared from 1µg of constitutional or neoplastic DNA and hybridize to a custom pool of oligonucleotides targeting genomic regions as previously described using the SureSelectXT enrichment system on a Bravo liquid-handling instrument (Agilent)[71]. Following capture, samples will be barcoded with 48 different indexed primers. The pooled samples are sequenced on a single lane of a HiSeq flowcell (Illumina) with 2x101bp paired end reads and a 7bp index read to allow for de-multiplexing and binning of individual samples. Single nucleotide variants and insertions and deletions will be detected as previously described with some updates in the bioinformatics pipeline [72, 73]. Deletions and duplications of exons will be detected by a combination of depth of coverage and split read analysis as previously described, supplemented with additional alignments generated by SLOPE[73, 74]. 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, analyses of NHEJ and other modifying genes, genomic scarring, or other somatic tests by Dr. Swisher's lab will be added to complement the determination of HR deficiency.

9.1.1.3 Shipping of Specimen(s)

Refer to the Specimen Requirement Table above and Appendices I, J and L.

9.1.1.4 Site(s) Performing Correlative Study

BROCA-HR will be performed by the laboratory of Dr. Elizabeth Swisher at the University of Washington (Seattle, WA).

9.1.2 Whole exome sequencing (WES; Integrated) and Whole transcriptome sequencing (WTS; Integrated)

9.1.2.1 Collection of Specimens

Refer to the Specimen Requirement Table above and Appendices I, J and L.

9.1.2.2 Handling of Specimens

We will make use of our CLIA-certified whole exome sequencing process for this proposal. We will provide variant calls within three weeks from sample receipt. We describe data generation steps below:

CLIA Portal. We have designed a portal through which information on patient samples can be directly entered and downstream results can be obtained. The following information is received securely through the portal:

- **Test Requisition Submission**: All test requests for the Clinical Sequencing are received through the CRSP Client Portal. An authorized individual representing either a requisitioning physician or referring CLIA-certified laboratory may submit test requisitions via the CRSP Portal. Once the pertinent information for the requisitioning individual (i.e., NPI & medical license numbers) or entity (CLIA certificate number) has been verified, the client will be supplied with the information (username/password) required to access the CRSP Client Portal. Submission of a test requisition through the CRSP Client Portal ensures that all required requisition elements (e.g. Patient and sample information and identifiers) are completed and are in an acceptable format.
- **Patient Information:** Patient information will be de-identified to the sequencing center. We will store only the information provided and utilize IDs assigned by the clinical centers. We note that for our standard test requisitions we have made available a portal through which physicians can supply patient identifying information that will be stored securely in a compliant manner. This information is supplied in the form of a unique alphanumeric identifier (supplied by the requisitioning individual/entity) or the more standard collection of personal identifiers (e.g. first name, last name, date of birth, address, telephone number). The requisitioning individual/entity also completes an attestation that the patient or legal representative has been informed of the potential risks and benefits of undergoing genetic testing and has consented to such testing
- **Sample Information.** The type of sample (DNA, EDTA-anticoagulated whole blood or Saliva) being submitted for testing will be supplied. If a unique alphanumeric patient identifier is being used, a distinct sample identifier will also

be supplied. Finally, the sample collection date will also be noted on the test requisition form.

Sample management and QC. Sample handling will be performed by the CLIA-certified lab within the Broad Institute's Genomics Platform and includes an industry-grade high throughput registration, processing, and tracking system for biological samples. The system includes multiple points of quality control (i.e., sample quantitation, tracking, and genetic fingerprinting), allowing us to receive and process an average of 16,000 samples per month. On arrival, each sample is assigned a unique bar code and entered into a validated database for sample analysis coupled to a bar code tracking system that records sample information (e.g., source, histology, clinical data), nucleic acid quality control information (e.g., genotyping, PCR), location information (e.g., freezer, shelf, rack), and project information. The database is linked directly to the LIMS systems for array and sequencing analysis.

For each DNA sample received, we will perform the following steps: Our optimized fingerprinting and WES processes require 50 to 100 ng input DNA. We will perform triplicate PicoGreen® DNA quantitation, and sample a subset of DNAs to verify high molecular weight DNA by a gel assay. By genotyping a panel of 127 highly polymorphic SNPs (including SNPs on chromosomes X and Y), a unique genetic *'fingerprint'* is generated for each sample. These genotypes are stored in the sample-tracking database and compared to genotypes obtained from whole exome sequencing to ensure integrity of sample handling and tracking from sample receipt through library sequencing.

Targeting the exome by hybrid selection. As described above, we will utilize whole exome targeting reagents from Illumina to prepare the sample libraries. The Illumina targeting process employs capture principles similar to those we developed and licensed to Agilent Technologies for the SureSelect® hybrid selection method but uses DNA instead of RNA oligonucleotides or baits for target capture. As discussed above the 'Rapid Capture Exome' content was co-developed with Illumina. Our own proprietary process enhancements to the 'Rapid Capture Exome' protocol makes use of these capture reagents along with our OneWell 'with-bead' library construction protocol and a specialized dual-indexing step for an extra level of contamination control. Briefly, our fully automated LIMS-tracked process begins with 100ng of Picogreen-quantified genomic DNA (in special cases as little as 50 ng of DNA). The genomic DNA is fragmented, using Covaris acoustic shearing, to the desired size of 150bp. Fragments are selectively bound to SPRI magnetic beads, followed by clean-up or washing steps, end repair, A-base addition, and indexed dual-adapter ligation. Following these steps the prepared DNA fragments are eluted from the SPRI beads and PCR amplified, generating 'pond' libraries ready for downstream hybrid capture. Pools of 12 indexed pond libraries then undergo two rounds of hybridization and 'capture' in which the pond pools are hybridized to the biotinylated exome baits, captured on streptavidin beads, washed at high stringency to remove off-target hybridizations, and then eluted from the SPRI beads. This process hybridization, washing, and elution is repeated once more and, following the second elution step, captured targets are PCR amplified, cleaned up one final time, and then submitted for sequencing.

Production Sequencing. Following targeting, libraries will be quantified (via Picogreen), normalized, and pooled. The resulting pool will be qPCR assayed and loaded onto flow cells for cluster amplification. All of these steps are part of Broad's standard Illumina library construction process which includes numerous QC steps: verification of all liquid handling instrumentation prior to each run using fluorescent dyes, QC of all critical reagent lots, auditing of vendor issued QCs for all other reagents, regular training verification of personnel, and other in-process QCs including specifically designed qPCR assays to verify loading concentrations.

We propose to use the HiSeq2500 for sequencing in this project. We have demonstrated failure rates of less than 10%, yields per flowcell of 130 Gb with run times of 27 hours for 2x101 runs, and have already produced over forty (40) terabases of data with the HiSeq2500. The HiSeq2500 fits seamlessly into the Broad sequencing laboratory and analysis pipelines and greatly simplifies the workflow and time in the lab with on-board cluster generation and reduced chemistry and imaging cycle times. Four (4) exome libraries are mixed or multiplexed and loaded per flow cell lane. We generate 5 Gb of sequence for each library. Real-time monitoring of many quality metrics, including the following is used to ensure exquisite control of the production line:

- **On-target sequence yield.** A major inefficiency of all massively parallel targeting approaches is the inability to precisely and uniquely capture (to the base pair) the target of interest. We have made a number of improvements to our production protocol (such as blocking agents against sequencing adaptors) which have resulted in routine on-target proportion of ~ 90% of reads.
- **Percent-target coverage ≥20X.** We require the baseline coverage to be >80% of targets to be covered at over 20X across the target region. This level of coverage typically results in ~100X average coverage across the exome, though higher levels of coverage can be achieved with additional sequencing.
- **Non-duplicate reads.** Observation of duplicate reads (reads with the same start and stop sites) indicates that the same molecule has been sequenced multiple times. This can mislead SNP calling algorithms, since the same molecule-specific (PCR or other) error can erroneously be counted as independent observations. We found that PCR upstream of selection can lead to a high degree of duplication, likely from bottlenecking of input material. Our current protocol is stable at 5-10% read duplication (duplicated reads are removed bioinformatically at BAM aggregation) and an increase in this measure signals issues with library preparation.
- **Contamination check.** As an additional layer of process control and test accuracy, we routinely apply a set of algorithms called '*verifyBamID*' to every sequencing dataset. *VerifyBamID* is a piece of software that detects possible sample mixture from population allele frequency only, which may be particularly useful when the genotype data is not available. Specically *VerifyBamID* verifies whether the reads in a particular file match previously known genotypes for an individual (or group of individuals), and checks whether the reads are contaminated as a mixture of two samples8. Using a mathematical model that relates observed sequence reads to a hypothetical true genotype, *verifyBamID* determines whether sequence reads obtained from the processing of a given sample match a particular individual or are more likely to be contaminated, derived from a closely related individual, or derived from a completely different individual.

In the rare instance when initial sequencing efforts fail to provide sufficient sequence coverage, additional sequence and coverage will be generated using the same rapid turn-around time exome express processes.

Data analysis

The CSRP's analysis pipeline consists of a large number of tools designed to detect different types of genomic events (Figure 1): (i) Point mutations (MuTect – Cibulskis et al.,; (ii) small insertions and deletions (Indelocator – Sivachenko et al.); (iii) rearrangements (dRanger – Lawrence et al.) and their exact breakpoint (BreakPointer); (iv) Copy-number changes (CapSeg– Carter et al.,); (v) Purity and ploidy, absolute copy-number and clonal/sub-clonal mutations (ABSOLUTE) (vi) Pathogen discovery (PathSeq); and finally (vii) we annotate all these genomic events with their effect on proteins, their relationship to disease, overlap with known cancer genes or pathways, potential functional effects using our tool Oncotator (Ramos et al., submitted; www.oncotator.org). The output of this pipeline is a set of VCF files (one per patient) and corresponding MAF file with all annotations. As of May 2014, MuTect and Indelocator have been validated in the CLIA process.

The CSRP's tools are of the highest quality in the field and were used to analyze a large number of cancer projects (references available upon request). For example, comparison of MuTect (CSRP's mutation caller) to other commonly used tools demonstrated that it is vastly superior (much more sensitive for any given false-positive value) (Figure 1). Finally, the Broad Institute is developing tools to take all types of alterations in a patient's tumor and prioritize the events with respect to clinical-relevance. These are then presented in a comprehensive report. Other tools that are being developed are aimed at analysis of sub-clonal composition of tumors and their evolution in multiple tumor samples (e.g. longitudinal samples, primary/metastases, primary/relapse etc.). These tools can estimate the number of macroscopic sub-clones and the fraction of cancer cells that they represent and when multiple tumors are analyzed the tools can also detect evolution of sub-clones (Landau, Carter, Stojanov et al.)

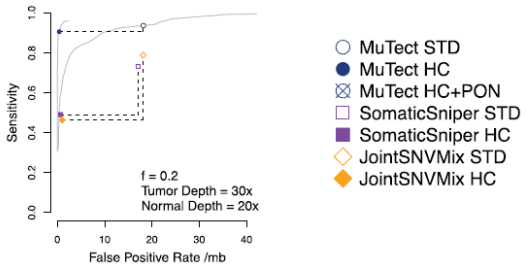


Figure 1 Receiver operating characteristic (ROC) curve for MuTect, for mutations at allele fraction of 0.2 and at 30x sequencing depth. Results are shown for Standard filtering (STD) and High-Confidence (HC). Results for two leading tools in the field, SomaticSniper and JointSVNMix are provided showing significant improved sensitivity for MuTect compared to the other tools.

Transcriptome Sequencing (RNA-seq)

We will also generate transcriptome sequencing using tumor RNA obtained from biopsies. RNA-seq may provide insights into overexpressed genes, chimeric transcripts (possibly indicative of underlying structural genomic rearrangements), and/or alternatively spliced variants. Thus, application of RNA-seq to serially obtained biopsies may provide useful

information about dysregulated pathways or networks not evident from somatic genetic analysis, pharmacodynamic changes caused by drug action, adaptive cellular responses to drug target inhibition, and "non-genetic" resistance mechanisms. As with WES, the Broad Institute has developed considerable "production-scale" expertise in RNA-seq sequencing. As the production center for the Genotype Tissue Expression (GTEx) project (http://commonfund.nih.gov/GTEx/), the Broad Institute has developed many RNA-seq protocols. In addition to the GTEx project, the Broad also produced RNA-seq data for the entire Cancer Cell Line Encyclopedia (CCLE). Over the past two years, the Broad Institute generated RNA-seq data for over 3,000 samples. Through application of automated fluid-handling techniques and process optimization, they created an RNA-seq sample preparation pipeline that can handle 192 samples per week at current demand levels.
Illumina's TruSeq method affords robust performance in terms of RNA input and sequencing library complexity. This method allows for input RNA amounts as low as 250-500 ng and is automated for high-throughput production. To generate RNA-seq data, polyA+ RNA will be isolated in the Genetic Analysis Platform at the Broad Institute. Next, strand-specific cDNA libraries will be generated. Each cDNA library will be sheared by sonication, paired-end adapters for Illumina sequencing will be added, and Illumina sequencing libraries will be prepared following established protocols. Each sample will be subjected to Illumina sequencing using an Illumina HiSeq instrument, producing ~101 bp paired-end reads. RNA-seq data will be analyzed by the Computational Biology Core.

As with WES, the Broad Institute has developed considerable "production-scale" expertise in RNA sequencing. Illumina's TruSeq method affords robust performance in terms of RNA input and sequencing library complexity. This method allows for input RNA amounts as low as 250-500ng and is automated for high-throughput production. Algorithms to identify RNA-based features including alternative splice variants, novel fusions and aggregate gene expression changes (CuffLinks/CuffDiff) will be applied to RNA-seq data.

9.1.2.3 Shipping of Specimens

Refer to the Specimen Requirement Table above and Appendices I, J and L.

9.1.2.4 Site Performing Correlative Study
WES and Transcriptome sequencing will be performed by the Center for Cancer Precision Medicine at the Broad Institute, Cambridge, MA.

9.1.3 **Plasma Angiome (Integrated)**
9.1.3.1 Collection of Specimen

Biomarker assays are time sensitive. Samples must be processed within **one** hour of collection. Complete the Blood Requisition Form (Appendix B of lab manual) and insert a copy of with shipment.

Required material:

- 10 mL purple/lavender-top EDTA-containing vacutainer tubes (BD Vacutainer, Catalog no. 366643)

- clear 15ml polypropylene tubes
- 2ml cryovials
- Labels designed for low temperatures (e.g., Cryo-Tag brand)

Collection:

1. Draw blood into one 10ml lavender top (K_2EDTA) tube (BD Vacutainer, Catalog no. 366643)
2. Invert tubes 10 times to mix blood
3. Centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
4. Remove plasma from each tube and transfer equally into two separate clean 15ml polypropylene tubes
5. Repeat centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions).
6. Aliquot approximately 1.0ml of plasma from each tube into each 2.0ml cryovial. A total of 5 capped cryovials are needed for EDTA plasma.
7. Label tubes with the following information (using a Sharpie or Cryopen):
    - Protocol Name
    - Subject Study Number
    - Subject Initials
    - Sample Date and Time
    - Sample Type (EDTA plasma)
    - Cycle #
8. Vials should be frozen at -80ºC immediately in an upright position and kept at -80ºC until shipment.
9. As plasma samples are analyzed in a retrospective manner, samples should be stored at the other sites outside Yale and shipped in batches at a later time to be agreed with the analyzing laboratory.
10. Complete the Plasma Biomarker Sample Shipping Form (Angiogenesis and Inflammation Markers) (Appendix B of lab manual) and insert a copy of with shipment.

9.1.3.2 Handling of Specimens

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.

Samples should be processed on site to obtain plasma and then shipped on dry ice. Biomarker assays are time sensitive, and samples should be stored on ice and processed within four hours of collection. Instructions for processing and labeling samples are below:

9.1.3.3 Shipping of Specimen

Instructions for packing and notifications for shipment follow:

- Agree to the timing of shipment with receiving laboratory.
- Use at least 5 kg dry ice for overnight delivery. The amount of dry ice may have to be increased if a large number of samples are sent or for a large shipping container.
- Samples should be placed upright in cryoboxes containing inserts.
- Include a completed Plasma Biomarker Sample Shipping Form for Markers of Angiogenesis and Inflammation (see Appendix B of lab manual) itemizing the contents of the shipment. A photocopy should be maintained with study records at each site.
- Place any paperwork in a plastic Ziploc bag.
- Send an email notification to the receiving lab with tracking number, and attach electronic version of completed Biomarker Sample Shipping Form to andrew.nixon@duke.edu and the study coordinator (email tbd).
- All samples must be shipped on dry ice by overnight delivery Monday through Wednesday (no holidays in the same week) to the following address:

Phase I Biomarker Laboratory
Dr. Andrew Nixon
Duke University Medical Center
395 MSRB, Research Drive
Durham, NC 27710
Phone: (919) 681-2239
Email: andrew.nixon@duke.edu

9.1.3.4 Site(s) Performing Correlative Study

Plasma angiome will be performed by the laboratory of Dr. Andrew Nixon at Duke University Medical Center (Durham, NC)

10. STUDY CALENDAR

In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Screening	Post Reg	Cycle (C) 1 **(=28 days)**			C 2			C3 and later	Off Study
	Day -27 to 0	D-6 to 0	D1	D 15 +/-3 days	D 22 - 28	D 1 +/- 3 days	D15 +/- 3 days	D 22 -28	D 1 +/- 3 days	
ARM A: Cediranib and Olaparib @X			X ---------->							
ARM B: Olaparib			X ---------->							
Home BP monitoring **(Arm A only)**[1]			X ---------->							
Informed consent	X									
Registration and Randomization	X									
Tumor Biopsies [2]		X[2a]			X[2b]					X[2c]
Germline BROCA		X								
Research Blood (Angiome)			X			X			X	
Demographics	**X**									
Medical H&PE / VS / PS/ Con meds / Tox assessment / Weight	X		X	X		X	X		X	
Height	X									
Hematology[3]	X		X	X		X	X		X	X
Serum chemistry[3]	X		X	X		X	X		X	X
Urine Protein/Creatinine Ratio[3]	X		X[8]	X[8]		X[8]	X[8]		X[8]	X[8]
INR and PTT [4]	X				X					
TSH and free T4	X								X[5]	
PSA	X					X			X	
Testosterone	X									
Tc99 Bone Scan	X							X[6]		
CT/MRI Abdomen and CT Chest	X							X[6]		
CT Neck (if clinically indicated)	X							X[6]		
ECG[3]	X									
Echo[7]	X									

FOOT NOTE:
1: patient must be advised to monitor home blood pressure twice a day for at least 8 weeks. Once deemed stable, then it may be reduced to once a day.
2: Tumor biopsy is mandatory at pre-treatment and during the 4th week.
2a: The baseline biopsy will be performed after registration/randomization, and within a maximum of 1 week, prior to the start of the protocol therapy (i.e., cycle 1 day 1). The protocol therapy should begin within 7 days after the

biopsy unless any concern by the treating investigator, in which case, the case must be discussed with the overall Study PI, prior to starting the therapy.
2b: On-treatment biopsy will be done during the 4th week of the study. While no stoppage of the study drug(s) is required for any needle biopsy, if any safety concern based on clinical factors, the study drugs may be held before and after the biopsy, at the discretion of the treating investigator after discussing with the overall Study PI.
2c: Post-progression biopsy is optional. Patients progressing on cediranib/olaparib or olaparib monotherapy may undergo a progression biopsy within 4 weeks from the last dose of the study treatment, or prior to the starting the subsequent therapy, whichever comes first.

Important Note:
- liver metastasis biopsy is allowed. Caution must be taken given the risk of post-procedural hemorrhage.
- If feasible, the on-treatment biopsy and progression biopsy should be taken from the same tumor lesion as the baseline biopsy. If not feasible, inform Study PI.

3: See the relevant subsections of 10.1 below.
4: Required within 7 days prior to the biopsy. See sections 10.1.2 and 5.2 for guidance for those on anticoagulation therapy.
5: For patients on the combination arm only, monitor **after every 2 cycles** throughout the study or earlier if clinically indicated.
6: See Section 11. Tumor reassessment will be time-based, and not cycle-based, with CT or MRI of Abdomen and Pelvis, CT scan of Chest, (CT neck if clinically indicated), and Tc99 Bone Scan, performed once every 8 weeks starting with the first restaging scan for the first 24 weeks of the study, then every 12 weeks (+/- 7 days) thereafter, and when clinically indicated.
7: See section 10.1.7 below.
@X: patients on olaparib monotherapy arm will have an option of cross-over. See the Section 5.6 Criteria for cross-over. When crossed over, patients will follow the schedule as shown here beginning D1, post-cross-over cycle 1. Biopsies are highly encouraged, especially pre-cross-over, but this is optional.
8: Only for patients on the combination arm.

10.1 Laboratory and Cardiac Safety Assessment

Any clinically significant abnormal laboratory values should be reported as clinically indicated and recorded on the eCRF.

10.1.1 Hematology test include the following and should be performed per study calendar and when clinically indicated.
- hemoglobin,
- red blood cells [RBC],
- platelets,
- mean cell volume [MCV],
- mean cell hemoglobin concentration [MCHC],
- mean cell hemoglobin [MCH],
- white blood cells [WBC],
- Absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and
- Absolute neutrophil count or segmented neutrophil count and Band forms.

If absolute differentials not available, please provide % differentials.

10.1.2 Coagulation test include the following and should be performed per study calendar and when clinically indicated.

- Activated partial thromboplastin time (aPTT)
- International normalized ratio (INR)

- **NOTE**: Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully **at least once per week** for the first month, then monthly if the INR is stable. See the Section 5.2 for the guidance for patients on anticoagulation therapy.

10.1.3 Biochemistry test include the following and should be performed per study calendar and when clinically indicated:

- Na, K, Chloride, Bicarb, BUN, Cr, Glucose, Calcium, Magnesium, Phosphorus, Albumin, Total Protein, Alkaline Phosphatase, ALT, AST, Total Bilirubin, LDH.

10.1.4 Urine Protein:Creatinine (UPC) Ratio should be performed in all patients for eligibility. Only those on the cediranib + olaparib arm are required to check UPC while they are on treatment.

10.1.5 **Bone Marrow and Blood Cytogenetic Analysis** should be considered ***if*** a patient develops **prolonged** hematologic toxicities as **defined** in section 6.1.1.3. These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

10.1.6 **Resting 12-lead ECG:**

Two 12-lead ECGs within 24 hours are required within 14 days prior to registration per eligibility criteria 3.2.12, and when clinically indicated after registration/randomization.

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

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

10.1.7 **Echocardiogram Assessment**

For eligibility purpose, echocardiogram is required **if** a potential candidate has the risk factors for developing potential cardiac toxicities from cediranib as defined in section 3.1.16.

For patients in combination arm only, echocardiogram is required **after every 4 cycles if the subject has the cardiac risk factors** as defined in section 6.1.3.3, or anytime if clinically indicated.

11. MEASUREMENT OF EFFECT

Tumor reassessment will be time-based, and not cycle-based, with CT scan or MRI of Abdomen and Pelvis, CT scan of Chest, and Tc99 Bone Scan, performed once every 8 weeks (+/- 7 days) for the first 24 weeks, then every 12 weeks (+/- 7 days) thereafter, 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 version 1.1. However, if a patient discontinues study treatment for any reason other than progression, imaging studies should continue every 8 weeks (+/- 7 days) on the protocol-outlined schedule until progression, or earlier if clinically indicated.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every *8* weeks. In addition to a baseline scan, **confirmatory** scans should also be obtained in **4 - 6 (not less than 4) weeks** following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

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

Evaluable for objective response. All patients with **measurable disease** present at baseline who have started the study treatment 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.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All

tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

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

11.1.3 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status

change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Bone Metastasis on Tc99 Bone Scan

Per PCWG2 [75]and PCWG3 [76] guideline, progression by bone scan is determined if any of the following is met:

(a) The first bone scan with greater than or equal to (>=) 2 new lesions compared to baseline is observed in less than (<) 12 weeks from randomization and was confirmed by a second bone scan taken >=6 weeks later showing >=2 additional new lesions (a total of >=4 new lesions compared to baseline), OR

(b) The first bone scan with >=2 new lesions compared to baseline was observed in **>=12** weeks from randomization and the new lesions were verified on the next bone scan >=6 weeks later (a total of >=2 new lesions compared to baseline);

11.1.4.4 Evaluation of Best Overall Response

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

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

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.				

** Only for non-randomized trials with response as primary endpoint. *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

11.1.5 PSA response

PSA response will be defined by PSA decline $\geq$ 50% from baseline at any point, confirmed by a second value obtained 3 or 4 weeks later.

11.1.6 Duration of Response

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

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

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

11.1.7 **Radiographic Progression-Free Survival (rPFS):**

The time interval from randomization to the first occurrence of any one of the following:

A. Progression by bone scan if

(a) the first bone scan with greater than or equal to (>=) 2 new lesions compared to baseline was observed in less than (<) 12 weeks from randomization and was confirmed by a second bone scan taken >=6 weeks later showing >=2 additional new lesions (a total of >=4 new lesions compared to baseline), OR

(b) the first bone scan with >=2 new lesions compared to baseline was observed in >=12 weeks from randomization and the new lesions were verified on the next bone scan >=6 weeks later (a total of >=2 new lesions compared to baseline);

B. Progression of soft tissue lesions measured by computerized tomography (CT) or magnetic resonance imaging (MRI), progression defined by RECIST v1.1

C. Death from any cause.

Participants alive without disease progression are censored at date of last disease evaluation.

11.1.8 Overall Survival

Overall survival is the time interval from randomization to the date of death due to any cause, or censored, at date last known alive.

11.1.9 PSA Response Rate:

Proportion of patients with a PSA response among those who are evaluable for response to an assigned therapy. The patients who were registered with a baseline PSA of 1.0ng/mg or greater and with rising PSA as defined in section 3.1.1.4, will be considered for evaluable for PSA response.

11.1.10 Objective response rate:

Proportion of patients with an objective response as defined by RECIST v1.1 among those who are evaluable for response to an assigned therapy. An objective response is defined by either PR or CR by RECIST v1.1.

11.1.11 Response Review

All objective responses will be reviewed by exert radiologists of the participating sites. No independent review is planned.

11.1.12 rPFS cross-over

The time interval from the start of the combination therapy at cross-over to the first occurrence of radiographic progression, defined in 11.1.7, or death from any cause

11.1.13 PSA response rate (cross-over)

A proportion of crossed-over patients with a PSA response (greater than or equal to 50% decline from the PSA at pre-cross-over

11.1.14 Objective response rate (cross-over)

Proportion of patients with measurable disease at pre-cross-over, who achieved an objective response (PR or CR) as defined by RECIST v1.1.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

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

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

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

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

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role

or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

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

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

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

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

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

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

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

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

12.3 Collaborative Agreements Language

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained

as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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

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

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

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

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed

for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is an open label randomized phase II study for patients with metastatic castration resistant prostate cancer, comparing the combination of cediranib and olaparib to olaparib monotherapy.

The primary objective of the study is to assess the clinical activity of the combination of cediranib and olaparib, as measured by radiographic progression free survival (rPFS), as compared to olaparib monotherapy in patients with mCRPC. Radiographic Progression Free Survival (rPFS) is the time interval from random assignment to the date of the first occurrence of disease progression or death, whichever occurs first. See section 11.1.7 for the definition for this study. Patients will be randomized in 1:1 ratio to either of the two arms. Patients randomized to the olaparib monotherapy arm will have the opportunity to receive the combination of cediranib and olaparib upon progression.

13.2 Sample Size/Accrual Rate

We consider a median rPFS of at least 8.8 months for patients treated with the combination of cediranib and olaparib as clinically promising (Ha: rPFS of the combination arm is superior to that of the olaparib monotherapy arm), relative to the expected median rPFS of 4.8 months associated with olaparib monotherapy (Ho: rPFS for the combination arm is at best, equivalent to that of the olaparib monotherapy arm). This corresponds to observing a hazard ratio of 0.55 (combination arm: olaparib monotherapy arm). The sample size estimation was completed using the log-rank test. With the proposed sample size of 84 (42 patients per arm), it provides at least 90% power to detect a 4-month improvement of rPFS for the combination arm with one-sided type I error = 10%. The assumptions of this calculation are the estimated accrual time = 12 months, the additional follow-up time = 14 months, and the accrual rate = 7 patients per month. Assuming the drop-out rate is about 5% - 7%, **a total sample size of 90 (45 per group)** has excellent power to detect a clinically

The expected median rPFS 4.8 months in the olaparib is based on the weighted average rPFS data from the TOPARP trial (Mateo et al. NEJM 2015). The authors did not report the overall rPFS of the study patients. Instead, they reported the rPFS of 2.7 months in biomarker negative patients (~70%) and 9.8 months in the biomarker positive patients (~30%). Based on these, we estimated that the average rPFS would be approximately 4.8 months. In our study, we will consider 4-month improvement in rPFS as clinically significant, which corresponds to HR0.55. We feel that, based on the results of contemporary positive and negative mCRPC trials (Morris M. et al. JCO 2015; Sternberg C. JCO 2016; Saad F. Lancet Oncol. 2015), rPFS of 0.55 is an acceptable measure to determine if the combination warrants further clinical development or not. Furthermore, a 4-month improvement in rPFS would indicate that there would be in average 2 staging scans to substantiate a radiographic response or progression.

The primary analysis is based on comparing rPFS between the arms (in the overall study population, regardless of mutation status): The final analysis is scheduled when 74 progressions/deaths are observed, and the suggested futility analysis would happen when 37 progressions/deaths are observed (half of the total required); at that point, if the control arm is doing better than the experimental arm (in terms of rPFS), the study would stop. It is expected that we will enroll at least 7 patients per month, based on accrual rate in each participating institution. This study will further be open to enrollment, ETCTN-wide

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	3	0	5	**8**
Asian	0	6	0	3	**9**
Native Hawaiian or Other Pacific Islander	0	3	0	1	**4**
Black or African American	0	26	0	6	**32**
White	0	25	0	7	**32**
More Than One Race	0	2	0	3	**5**
Total	**0**	**65**	**0**	**25**	**90**

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13.3 Stratification Factors

None

13.4 Analysis of Primary and Secondary Endpoints

13.4.1 **Primary Analysis:**

We will use intension to treat (ITT) analysis for the primary and secondary endpoints. The primary endpoint is radiographic progression free survival (rPFS). Radiographic Progression Free Survival (rPFS) is the time interval from random assignment to the date of the first occurrence of radiographic disease progression or death, whichever occurs first. See section 11.1.7 for the definition for this study. The primary analysis will be based on "intent-to-treat." All patients who are enrolled and randomly assigned to treatment will be included in the analysis and will be analyzed in the arms to which they were randomized.

For the primary endpoint data analysis, i.e., rPFS, the two study arms will be compared for rPFS survival with Kaplan-Meier estimates and log-rank tests. The Rothman confidence interval (CI), which is based on Greenwood's variance, Thomas and Grunkemeier CI, and the simultaneous confidence bands by Nair and Hall and Wellner, will be reported. In addition, the possible confounding variables will be compared for survival with log-rank test.

13.4.2 **Secondary Analyses**

The primary objective of the secondary analysis is for hypothesis generating instead of hypothesis testing. No formal power analysis and sample size estimation was conducted.

Overall Survival (OS)
OS is defined at the time between randomization and death due to any cause (or last contact for surviving patients and those lost to follow-up). We will use the rank preserving structure failure time model for the OS analysis.

Objective Response Rate (ORR)
ORR will be based a subset of patients with RECISTv1.1- measurable disease. The exact 95% confidence interval of ORR will be reported based on the binomial distribution. The multivariate data analysis will be completed using the logistic regression model. The adjusted p-value and adjusted 95% confidence interval will also be reported.

PSA Response Rate
PSA response will be defined by PSA decline from baseline > 50%, confirmed by a second value at 3-4 weeks later. PSA response rate analysis will be based on a subset of patients who had PSA progression prior to enrollment. The similar data analysis plan, as described for ORR, will be applied to PSA Response Rate.

Analysis Plan for Safety Data:

Safety will be measured by the risk of adverse events per NCI CTCAE v4.0 until March 31, 2018 and per CTCAE v5.0 beginning April 1, 2018. All subjects who received at least a dose of study medications will be included for safety analysis. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as percentages and frequencies for categorical parameters, will be presented. Adverse medical events will be tabulated. NCI toxicity Grade 3 and Grade 4 laboratory abnormalities will be listed and tabled.

BROCA-HR
A secondary objective is to evaluate association of homologous recombination DNA repair deficiency (HRD) with the clinical activity of the combination of cediranib and olaparib or olaparib monotherapy, as measured by rPFS, in mCRPC patients. HRD positive status is defined by presence of homozygous deletion or deleterious mutations inkey homologous recombination genes of DNA repair genes as analyzed by BROCA-HR test. We estimate the frequency of the positive biomarker (HRD positive) would be approximately 25% (Prichard CC et al. NEJM 2016; Robinson et al. Cell 2015; Mateo J et al. NEJM 2015).

The data analysis will be completed using log rank Test. The multivariate data analysis will be completed using the Cox PH model.

Whole Exome Sequencing and Transcriptome Sequencing
A secondary objective is to characterize genomic alterations by whole exome sequencing and transcriptome sequencing in mCRPC patients. This is an exploratory study and there are multiple potential outcomes we would want to derive from this analysis. This includes identification of biallelic loss of key DNA repair gene mutations (as determined by integrative mutation and copy number data that requires WES analysis), and mutational signatures for HR or NER that may impact response to therapy. In addition, we will study copy number variation, small indels, and structural variation. The biomarker data, e.g., whole exome sequencing and transcriptome sequencing, analysis will be completed using Lasso-based elastic net method. The elastic net method is a variable selection procedure by L1 and L2 penalized estimation that enforces variable selection and shrinkage simultaneously. The penalty parameter that controls the shrinkage of fixed terms and the variable selection will be determined by k-fold cross validation. Because of the limited sample size, the biomarker data analysis is for exploratory research only. The statistical analyses will be completed by either R 3.2.1 or SAS 9.4 statistical program in this project.

Plasma Angiome
An exploratory objective is to identify baseline predictive biomarkers for rPFS or response and to identify on-treatment markers of acquired resistance in men with mCRPC receiving either olaparib plus cediranib or olaparib alone. The data analysis will be completed using Lasso-based elastic net method. The elastic net method is a variable selection procedure by L1 and L2 penalized estimation that enforces variable selection and shrinkage simultaneously. The penalty parameter that controls the shrinkage of fixed terms and the variable selection will be determined by k-fold cross validation.

13.4.3 Rationale for biopsies

Paired biopsies will be required for all participants. The goal of the paired biopsies is to assess

interval changes in the biomarkers that will be critical for understanding the mechanisms of response and resistance to the cediranib and olaparib combination, compared with those to olaparib monotherapy.

Within the combination arm, we hypothesize that cediranib work in synergy with olaparib by downregulating the expression of DNA repair genes, leading to homologous repair (HR) deficient state, thus sensitizing the tumor to a PARP inhibition. The whole exome and transcriptomes sequencing will be performed in baseline tumor biopsies and on-treatment biopsies to see if there is down-regulation of mRNA transcripts in DNA repair genes after initiation of cediranib and olaparib combination therapy, and to see if this change correlates with response to the therapy. The comparison between the arms will be done by the subgroup analysis of their HR biomarker status.

For HR proficient patients (patients without germline or somatic mutations in DNA repair genes, determined by BROCA test), we expect to see significant difference in mRNA transcripts in DNA repair genes in the combination arm compared with olaparib monotherapy arm. In other words, there will be significant decrease seen in the combination arm from pre- vs on-treatment, but no significant decrease in the olaparib monotherapy arm. We assumed that 25% of the patients will have HR deficient (HRD) mCRPC and 75% HR proficient (HRP) mCRPC. Given our total sample size of 84 patients (See Section 13.2), we estimate that there will be approximately 63 HRP patients. With 1:1 randomization, we estimate that there will be approximately 31 and 32 HRP patients in the combination arm and olaparib monotherapy arm. Although there was no formal power analysis and sample size estimation conducted for this comparison, with the sample size of 30 per group, it provides at least 80% power to detect an odds ratio (OR) of 2.0 with one-sided type I error = 10%.

For HR deficient patients (patients with germline or somatic mutations in DNA repair genes, determined by BROCA test), we expect to see no significant difference in mRNA transcript in DNA repair genes between the two arms. As above, we assumed that 25% of the patients will have HRD and 75% HRP. Given our total sample size of 84 patients (See Section 13.2), we estimate that there will be approximately 21 HRD patients. With 1:1 randomization, we estimate that there will be approximately 11 and 10 HRD patients in the combination arm and olaparib monotherapy arm. This analysis is for hypothesis generating instead of hypothesis testing.

13.4.4 Futility Analysis for Early Stopping

The futility analysis will be based on the method proposed by Wieand et al. (Stat in Med 1994, p 1453). If after half events (50% of the targeted information) are observed and the observed hazard ratio for combination arm vs. single agent arm comparison favor the single agent arm, then the study will be closed to accrual.

Wieand's method is to analyze the data when half the required events have been observed. At that time, if the ratio of the observe event rate of the experimental regimen divided by the observed event rate of the standard regimen equals or exceeds 1, we would consider terminating the trial and concluding that an advantage for the experimental regimen has not been established. The advantages associated with this method including the following:

(1) It is "intuitively reasonable". Most investigators are ready to stop accruing patients to the regimen when a study is half over and there is no apparent (experimental) treatment benefit.
(2) The fact that there is only one early look is not a serious detriment, since early reporting of results is generally not as important as early termination of accrual.
(3) For any alternative satisfying the proportional hazards assumption, the loss of power associated with this design is minimal.

13.4.5 Safety Analysis for Biopsies

We will pilot a cohort of the first 6 patients assigned to either treatment arm, to make sure that the biopsies are performed safely and that adequate tissues are being obtained for the biomarker analysis. To this end, there will be an enrollment hold after the 6th patient gets enrolled. The enrollment will be held until the 6th patient undergoes the second biopsy, and is monitored for at least one week after the biopsy. At that point, the overall study principal investigator, translational co-principal investigators and the investigators from the participating sites will review the biopsies of the first 6 participants to discuss and confirm the safety and feasibility of these biopsies, and to obtain approval to continue with enrollment. If participating investigators are not available for this discussion, we will email them the relevant information and ask them to respond.

Examples of the significant adverse events related to the biopsy include:
- Grade 3 or 4, significant bleeding complication requiring transfusion or hospitalization.
- Grade 3 or 4 wound complication, such as poor healing limiting or delaying initiation of the study medication.
- Grade 3 or 4 wound infection/abscess formation requiring hospitalization and IV antibiotics.
- Grade 3 or 4 fistula formation.
  Other grade 3 or 4 adverse events deemed related to the biopsy that compromises the safety of the participants.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

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

13.5.2 Evaluation of Response

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

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

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

13.5.3 Evaluation of radiographic progression free survival

The analysis of the primary endpoint, radiographic progression free survival, will be based on an intent-to-treat basis. All patients who are enrolled and randomly assigned to treatment will be included in the analysis and will be analyzed in the arms to which they were randomized, even if there are major protocol treatment deviations or if they are ineligible.

The definition of rPFS is provided in 11.1.7. Participants alive without disease progression are censored at date of last disease evaluation. The statistical analysis plan is provided in 13.4.1

13.5.4 Evaluation of clinical activity to the combination therapy among those who have crossed over to the combination arm after progressing on olaparib monotherapy.

Patients who cross-over to the cediranib and olaparib combination will be followed per the study calendar, section 10. The following data will be collected and assessed.

- rPFS (cross-over): See section 11.1.12 for definition.
- PSA response rate (cross-over): See section 11.1.13 for definition.
- Object response rate (cross-over): See section 11.1.14 for definition.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B NEW YORK HEART ASSOCIATION CLASSIFICATIONS

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

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

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician

** At accustomed occupation or usual tasks

APPENDIX C-1 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.

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 _____.

APPENDIX C-2 PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD – 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, **cediranib (AZD2171).** 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:

Cediranib (AZD2171) 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. Cediranib (AZD2171) is metabolized by FMO1, FMO3 and UGT1A4 and may be affected by other drugs that strongly inhibit or induce these enzymes. Cediranib (AZD2171) 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). Cediranib (AZD2171) 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.
- Cediranib (AZD2171) 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 Cediranib (AZD2171) 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:

Cediranib (AZD2171) must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of FMO1, FMO3, UGT1A4 and P-gp." Cediranib

(AZD2171) inhibits enzymes "CYP 2D6 and 3A4, transport proteins BCRP, P-gp, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K and is highly protein-bound." These characteristics may change how other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Cediranib (AZD2171) can increase the risk of bleeding and interferes with wound healing. Let your doctor know if you recently had or are planning to have any surgery.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

June 2016

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental drug **AZD2171 (cediranib).** This clinical trial is sponsored by the NCI. Cediranib (AZD2171) 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.
- Cediranib (AZD2171) 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 _____.

APPENDIX D LIST OF MEDICATIONS PROHIBITED ON STUDY

The investigators must utilize the following frequently updated drug information references. All the patient's concomitant medications should be recorded and checked for potential drug interactions against the investigational agents.

Strong or moderate inhibitors or inducers of CYP3A4/5 **are prohibited** during the study.

1. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2
   See the examples of clinical inhibitors for P450-mediated metabolism (for concomitant use clinical DDI studies and/or drug labeling). The drugs listed under **Strong or Moderate Inhibitors** of CYP3A are prohibited.

   Plus, unless indicated in the website, the following medications are considered Strong or Moderate inhibitors of CYP3A:
   - **Strong CYP3A inhibitors:** itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir.
   - **Moderate CYP3A inhibitors:** ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil.

   A minimum washout period of **2 weeks** prior to cycle 1 day 1 is required for st**rong inhibitors,** and **at least one week** for **moderate inhibitors.**

2. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-3
   See the examples of clinical inducers for P450-mediated metabolism (for concomitant use clinical DDI studies and/or drug labeling). The drugs listed under **Strong or Moderate Inducers** of CYP3A are prohibited

   Plus, unless indicated in the website, the following medications are considered Strong or Moderate inducers of CYP3A:
   - **Strong CYP3A inducers:** phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort
   - **Moderate CYP3A inducers**: bosentan, efavirenz, modafinil.

   A minimum washout period of **4 weeks** prior to cycle 1 day 1 is required for **CYP3A inducers**. A minimum washout period of **5 weeks** prior to cycle 1 day 1 is required for **enzalutamide or phenobarbital**. Dihydropyridine calcium-channel blockers are permitted for management of hypertension.

APPENDIX E PILL DIARY FOR OLAPARIB MONOTHERAPY ARM

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.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Otherwise, do not make up the dose.

5. If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose.

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

OLAPARIB Take _____ (number) _____ mg and _____ (number) _____ mg tablets twice a day 12 hours apart after a light meal. You should avoid grapefruit juice while on study because grapefruit juice affects the metabolism of olaparib.						**NOTE**
Day	**Date**	**100mg**	**150mg**	**AM**	**PM**	
1	*1/1/15*	*0*	*2*	*7:00*	*7:00*	
1						
2						
3						
4						
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Patient's Signature: _____ Date: _____

Physician/Nurse/Data Manager's Signature _____ Date_____

APPENDIX F PILL DIARY FOR CEDIRANIB / OLAPARIB COMBINATION ARM

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 cediranib doses.
   If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Otherwise, do not make up the olaparib dose.
5. If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose.

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

CEDIRANIB Take ____ (number) _____ mg tablets once a day. Take on an empty stomach. Olaparib may be taken together in the AM.					**OLAPARIB** Take _____ (number) _____ mg and _____ (number) _____ mg tablets twice a day 12 hours apart after a light meal. You should avoid grapefruit juice while on study because grapefruit juice affects the metabolism of olaparib.						**NOTE**
Day	**Date**	**15mg**	**20mg**	**AM**	**Day**	**Date**	**100mg**	**150mg**	**AM**	**PM**	
1	*1/1/15*	*2*	*0*	*7:00*	*1*	*1/1/15*	*2*	*0*	*7:00*	*7:00*	
1					1						
2					2						
3					3						
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28					28						

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

APPENDIX F-1 SYMPTOM DIARY FOR CEDIRANIB AND OLAPARIB COMBINATION ARM

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

Study doctor's name is _____ The 24-hour number to call is _____

TWO most common side effects of cediranib and olaparib combination treatment are **elevated blood pressure** and **diarrhea**. In order to effectively manage your side effects, please watch for these side effects and complete this diary as below.

1. You must monitor and record your **blood pressure at least twice a day. CALL** your study doctor when your blood pressure **is greater than or equal to 140/90.** If so, you will need to take medication(s) to lower your blood pressure to below 140/90.
2. **Diarrhea** is bowel movements occurring **more often than normal**, or bowel movements that are **soft, loose, or watery**.
3. When you begin to have **diarrhea**, **CALL** your study doctor and **TAKE loperamide (Imodium®)** 2mg with every bowel movement until diarrhea stops, or 4mg initially if your diarrhea is more than 4 times than usual, and 2mg thereafter, with every bowel movement, until diarrhea stops. You are advised to **start "BRAT" diet**, made up of banana, rice, applesauce and toast, or the like). You will be given a patient information handout on diarrhea. https://www.cancer.gov/publications/patient-education/diarrhea.pdf.
4. **If your diarrhea does not improve after 24 hours** of loperamide and BRAT diet, ***or*** if you develop **any associated symptoms**, **CALL** your study doctor team again!

		Your GOAL blood pressure is <140/90		Blood Pressures medications	Write down your usual frequency of bowel movement before you begin this treatment: _____time(s) a day. ***Any associated symptoms***: feeling dizzy, fever Temperature ≥ 100.5^{O}, belly pain, blood in stool, or sore in rectal area?		Other notable findings.
Day	**Date**	**Morning BP**	**Evening BP**		**Number of bowel movement**	**Associated Symptoms?**	
1	*02/01/2017*	*120 / 62*	*112 / 60*	*e.g.) Lisinopril 40mg Atenolol 100mg*	*Call if you begin to develop diarrhea*	*Call if you develop any associated symptoms*	
1		/	/				
2		/	/				

3		/	/				
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30		/	/				
31		/	/				

Patient's Signature: _____ Date: _____

Physician/Nurse/Data Manager's Signature _____ Date_____

APPENDIX G SUGGESTED ORAL ANTI-HYPERTENSIVE 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. It is suggested that each agent's dosing should be maximized before being replaced or adding another agent class. Additional agent may be used prior to the maximal dose of the current agent if clinically deemed necessary.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	Yes (CYP450 unknown)
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	**Yes, but not CYP450**
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 and 2C9 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**

Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	CYP 3A4 substrate
α and β Blocker	labetalol	100 mg twice daily	200 mg twice daily	400 mg twice daily	Yes, but not CYP450
Diuretics	Hydralazine	10 mg four times daily	25 mg four times daily	50 mg four times daily	no
	Hydrochlorothiazide	12.5 mg AM daily	25 mg AM daily	50 mg AM daily	no
	Furosemide	20 mg daily	20 mg twice daily	40 mg twice daily	no
Nitrates	Isosorbide dinitrate ER	40 mg daily	40 mg twice daily	80 mg twice daily	CYP 3A4 substrate
	Isosorbide mononitrate ER	30 mg AM daily	60 mg AM daily	90 mg AM daily	CYP 3A4 substrate
Dihydropyridine Calcium-Channel Blockers (DHP CCB)	nifedipine XL	30 mg daily	60 mg daily	90 mg daily	CYP 3A4 substrate
	amlodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate

APPENDIX H RISK-BASED APPROACH FOR PATIENT MONITORING AND PROTOCOL DRIVEN MANAGEMENT

Hypertension Management

- 41% grade 3 hypertension rate on phase II cediranib/olaparib trial
  - CTCAE g1: SBP 120-139mmHg; DBP 90-89mmHg (monitor)
  - CTCAE g2: single anti-hypertensive
  - CTCAE g3: More than one anti-hypertensive
  - CTCAE g4: Life-threatening consequences (Hold cediranib)
- All patients should check **BP at least twice daily** for at least 8 weeks until stability is established.
  - Potentially longer if anti-hypertensive regimen adjustment needed
  - May also need more frequent monitoring if cediranib dose is held or altered.
  - Patients should keep BP diary and call study team for BP >140/90mmHg

Hypertension

- **Start anti-hypertensives for BP ≥ 140/90mmHg**
  - Preferred anti-hypertensives and examples
    - **Lisinopril** (start at 5-10mg, titrate up to 40mg daily)
    - **Losartan** (start at 25mg, titrate up to 100mg daily)
  - Beta-blockers
    - **Labetalol** (start at 100mg BID, titrate upto 400mg BID)
  - Dihydropyridine calcium channel blockers (CCBs)
    - **Amlodipine (**start at 2.5mg, titrate up to 10mg daily)
    - CAUTION: Can worsen proteinuria
- Titrate anti-hypertensives **every 12 to 24 hours** until BP <140/90mgHg
  - Review patient's BPs on weekly basis for first 8 weeks for compliance.

Aggressive management is KEY.
Start therapy early.
Manage BP aggressively.

Diarrhea

- **Start loperamide (immodium) as soon as diarrhea starts**
  - 2mg for grade 1, with 2mg with every bowel movement until diarrhea stops
  - 4mg for grade 2, with 2mg with every bowel movement until diarrhea stops
- Start BRAT (Bananas, Rice, Applesauce, Toast) diet
- **Persistent diarrhea despite 24 hrs of loperamide, requires dose hold**, with potential need for dose reduction.
  - 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

Aggressive management and patient counseling are critical.
Start loperamide and BRAT diet as soon as diarrhea occurs
Dose hold +/- reduction for persistent diarrhea symptoms

Toxicity Management

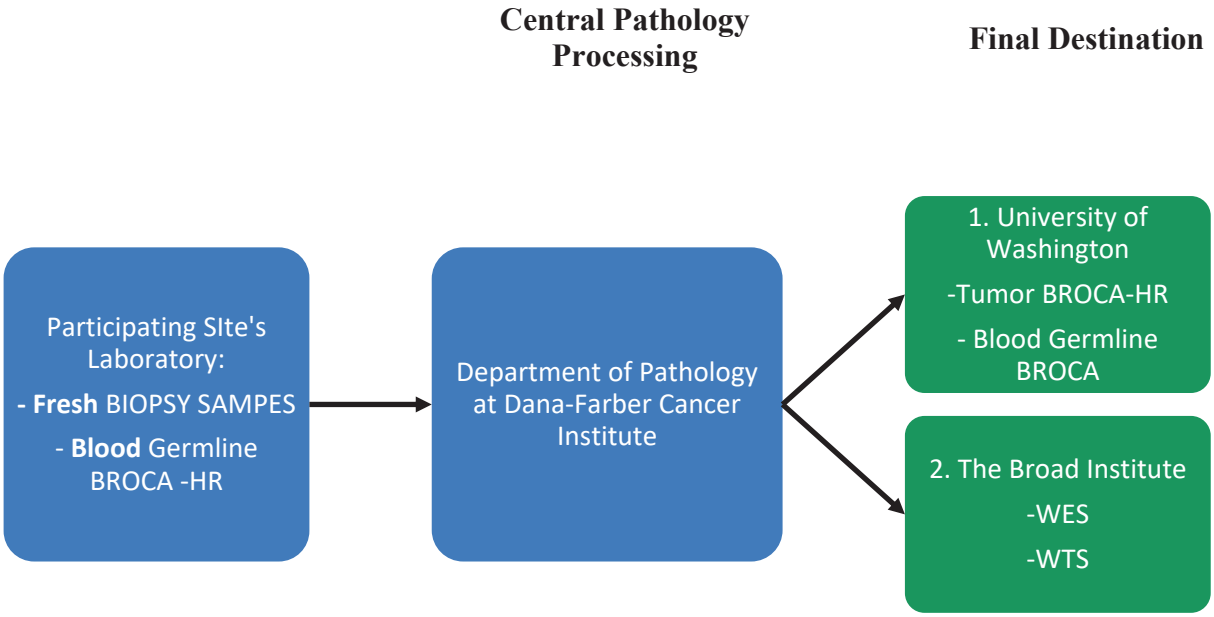
- Patients should be counseled regarding HTN and diarrhea side effects
  - Please **provide prescription for anti-hypertensive and loperamide** at cycle 1 day 1 visit
  - Consultant with cardiologist/ nephrologist can be helpful in controlling difficult to manage HTN particularly in patients with pre-existing hypertension
- Please do no hesitate to call/email with questions:

ETCTN-9984
Study Nurse: Shelby DeCarlo
Email: Shelby.decarlo@yale.edu
Study PI: Dr. Joseph W Kim
Email: joseph.w.kim@yale.edu

APPENDIX I STANDARD OPERATING PROCEDURE FOR COLLECTION AND PROCESSING OF BIOPSY TISSUE

1. TISSUE PROCESSING

Tissue Laboratory Flow:



HRD = Homologous recombination deficiency, WES=Whole exome sequencing, WTS=Whole transcriptome Sequencing, TILs=Tumor infiltrating lymphocytes, QIF=Quantitative Immunofluorescence.

The tissue/tumor collections will occur via an image-guided (CT scan or US-guided) needle biopsy of a soft tissue or bone lesion. Biopsy of soft tissue is preferred when possible. Blood samples will be drawn within 2 weeks of the biopsy to document an acceptable coagulation profile (INR ≤ 1.5, PTT ≤ 60, platelets > 50,000) as per institutional standard procedures. Heparin, low molecular weight heparin, aspirin, and other anti-platelet agents should be discontinued as per institutional standard procedures.

The baseline biopsy will be performed after registration/randomization, and within a maximum of 1 week, prior to the start of the protocol therapy (i.e., cycle 1 day 1). The protocol therapy should begin within 7 days after the biopsy unless any concern by the treating investigator, in which case, it must be discussed with the overall Study PI, prior to starting the therapy.

On-treatment biopsy will be done during the 4th week of the protocol therapy. While no stoppage of the study drug(s) is required for any needle biopsy, if any safety concern based on clinical factors the study drugs may be held pre and post biopsy, at the discretion of the treating investigator after discussing with the overall Study PI.

Post-progression biopsy is optional. Patients progressing on cediranib/olaparib may undergo a progression biopsy within 4 weeks from the last dose of the study treatment or prior to the starting the subsequent therapy, whichever comes first.

Soft Tissue Biopsies:
Soft tissue biopsies will be performed per institutional standards and/or operator preference. Preferred soft tissue biopsy sites include: lymph nodes, peripheral based liver lesions, exophytic soft tissue components associated with bone lesions, subcutaneous nodules, pleural-based lesions, and kidney lesions. An 18 gauge or larger is preferred for soft tissue biopsies. Cautionary Note: liver biopsy is allowed. Caution should be taken given the risk of post-procedural hemorrhage.

Bone Biopsies:
Bone biopsies will be performed per institutional standards and/or operator preference. Bone biopsies should not be performed on irradiated lesions. Preferred bone sites include the lumbar vertebrae, pelvic bones and long bones. Use of the OnControl® Biopsy System is preferred when safe and appropriate (pelvic bones). Given lower yield on bone biopsy special attention should be given to the following parameters which may correlate with tumor yield on bone biopsy:

- Size
- Degree of sclerosis
- Distance from the skin to the lesion
- Distance from the cortex to the lesion
- Presence of a bone scan correlate
- Area to target for biopsy (center versus periphery of the lesion)

Important:
For each tissue collection procedure, the intent is to acquire up to 6 needle cores for rapid freezing in OCT medium. Size of these biopsy cores can be variable (0.1-1.0 cm). While larger cores are preferable to optimize tumor capture, cores of any size should be processed. Long cores approximately >2cm can be split. A minimum of 3 cores is preferred. If feasible, the optional progression biopsy should be taken from the same tumor lesion as the baseline biopsy.

A. Pre-Biopsy Labeling of Tubes and Cryomolds
Research staff should communicate with the interventional radiology team in advance of the biopsy to ensure that requested specimens are collected

according to the laboratory manual. Coordination efforts with the interventional radiology and pathology teams will vary depending on the institution. It is advised to *arrive at the biopsy collection site at least 15 minutes ahead of the scheduled time to allow sufficient time to set up laboratory supplies and ensure rapid transport of specimens to the laboratory after collection.*

1. Label the metal molds or the plastic Tissue Tek™ standard-size cryomolds 1-8. This will identify which biopsy core was taken 1st, 2nd, 3rd, and etc.
2. Using pre-printed or hand-written labels, label plastic tissue cassettes (mega sized) with the following information on the front of the cassette (see Figure 1):
    - Biopsy date
    - Institution site
    - Patient ID
    - Biopsy core number (refers to the order in which cores were collected)
    - Clinical protocol number
    - Pre, 4-week, or post-tx

B. Collection of Biopsies

*This procedure should be performed within **20-30 minutes** of biopsy collection and tissue out of body. Please complete tissue requisition form (Appendix J). Record times using military time (24-h designation), for example specify 16:15 to indicate 4:15 PM. Please record the time from biopsy to freezing. Please try to stay close to 30 minutes. Procedures may vary depending on the institution. Bone and soft tissue biopsies will be processed by the same procedure as detailed below.*

1. Place a thin layer of prechilled OCT into a metal mold (or plastic cryomold).
2. Transfer freshly collected needle biopsy with the sterile needle or tweezers at one end and place the core on the bottom of the metal mold as flat as possible.
3. Fill a metal mold with a thin layer of prechilled OCT ensuring no air bubbles are present near the tissue.
4. Immediately transfer the mold to the prechilled metal plate on dry ice and wait for complete freezing.
5. Record time of collection and OCT frozen for each pass on the Image-Guided Needle Biopsy requisition form.
6. Repeat procedure for each separate biopsy (sequentially from #1 to #5).
7. After the OCT solidified, cut the edge of the cryomold to fit into the pre-labeled cassette before storage, if needed. Add a drop or two of OCT to cover any tissue exposed to air, and place on metal plate to freeze.Make sure to match the # on the mold with the pre-labeled cassette.

C. Storing of Biopsy Specimens

Return to the sample processing laboratory with the specimens, transfer cryopreserved biopsy specimens to a -80°C freezer. Complete the tissue requisition form and store until shipping. **Note any deviations from the laboratory manual on the requisition form.** Please ship frozen tissue on dry ice.

D. Shipping of Biopsy Specimens

Samples can be shipped within 24 hours of collection, on dry ice by express overnight courier. Shipping reservations must be made to allow delivery within 24hr prior to 2:00 PM next day. Call the receiving laboratory the day prior to shipping to confirm plan for receipt. **Do not ship on Thursday or Friday (NO WEEKEND DELIVERY)**. Please make sure that blood for germline DNA/RNA be shipped with biopsies on dry ice. Lank Center of Genitourinary Oncology at Dana-Farber Cancer Institute will receive the "Blood for Germline DNA/RNA" and store it at received labeled conditions (i.e refrigeration at 4^0 Celsius, etc) 'as is' (package intact and unopened), and will ship this package together with tissue nucleic acid to The University of Washington and The Broad Institute.

Dana-Farber Cancer Institute
Lank Center for Genitourinary Oncology
Attention: Tissue Biopsy for Olaparib/Cedirinib, Dr. Rosina Lis or Zhenwei Zhang
450 Brookline Avenue, DA1230
Boston, MA 02215
617-582-8757
Pager from outside DF/HCC: 617-632-3352
Pager #: 49274

Please send an e-mail notification 1 week prior to shipment with the delivery plan and again on the day of shipment with the tracking information to the following:
Zhenwei Zhang: Zhenwei_Zhang@dfci.harvard.edu

E. Processing of Specimens at Central Laboratory (Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute)

The central pathology processing laboratory will collect, process and prioritize specimens for further processing. Once tissue specimens are received to the laboratory, each core will be sectioned to generate an H and E slide to assess the tumor cellularity of the individual core. This will be documented on the Tissue Requisition Form **(Appendix J)**.

The cores with the most tumor cellularity (whether >30% or 10-30%) will be

utilized to isolate DNA/RNA. A minimum of 300 ng of DNA will be sent to University of Washington for BROCA-HR and HRD score. Additionally 1 cryovial containing 1mL of whole blood for germline DNA analysis will be sent to the University of Washington with isolated nucleic acid. A minimum of 400 ng of DNA and 400 ng RNA will be sent to The Broad Institute for whole exome and transcriptome sequencing. Additionally 1 cryovial containing 1mL of whole blood for germline DNA analysis will be sent to The Broad Institute with isolated nucleic acid.

Any remaining cores will be stored for future use.

Given necessity of ≥10% tumor cellularity of BROCA-HR analysis, cores with <10% tumor cellularity will not be processed for BROCA-HD or HRD scores and these patients will be counted as unevaluable.

F. Shipping of Specimens from the Lank Center of Genitourinary Oncology at Dana-Farber Cancer Institute to Final Destination

University of Washington
Samples can be shipped in batches once every month on dry ice by express overnight courier. Shipping reservations must be made to allow delivery within 24hr prior to 2:00 PM next day. Call the receiving laboratory the day prior to shipping to confirm plan for receipt. **Do not ship on Thursday or Friday (NO WEEKEND DELIVERY)**.

Dr. Elizabeth M. Swisher Lab
University of Washington
1959 NE Pacific St
Health Sciences Building K154
Seattle, Washington 98195-6460
Phone: 206-616-4296
Please send an **e-mail** notification 1 week prior to shipment with the delivery plan and again on the day of shipment with the tracking information to the following:

swishere@uw.edu

2. Procedure for Collection and Processing of Blood Specimens

A. Blood for Germline DNA Collection

Supplies:

- 21g ¾ inch Safety-Lok Blood Collection set (butterfly needle) with 12 inch tubing
- EDTA purple-top plasma tube

- Cryovials for transfer of samples from EDTA tubes
- Disposable transfer pipettes

Processing:

1. Fill the EDTA tube with 5 mL of blood. Gently invert tubes 8-10 times immediately.
2. Place EDTA tube on ice or 4 ^{0}C and process IMMEDIATELY.
3. Transfer 5 mL of blood into cryovials, 1.0 mL per cryovial. Freeze these vials immediately in -80 °C.

B. Blood for Germline DNA Shipment

Samples should be shipped with baseline biopsies, on dry ice. Shipping reservations must be made to allow delivery within 24hr, prior to 2:00 PM next day. Call the receiving laboratory the day prior to shipping to confirm plan for receipt. **Do not ship on Thursday or Friday**.

Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute will receive the "Blood for Germline DNA/RNA" and store it at received conditions 'as is' (package intact and unopened), and will ship this package together with nucleic acid to The University of Washington and The Broad Institute.

Dana-Farber Cancer Institute
Lank Center for Genitourinary Oncology
Attention: Germline DNA/RNA for Olaparib/Cedirinib, Dr. Rosina Lis or Zhenwei Zhang
450 Brookline Avenue, DA1230
Boston, MA 02215
617-582-8757
Pager from outside DF/HCC: 617-632-3352
Pager #: 49274

Please send an e-mail notification with the shipment tracking information to the following:
Zhenwei Zhang: Zhenwei_Zhang@dfci.harvard.edu

C. Blood for Angiome Collection

Biomarker assays are time sensitive. Samples must be processed within **one** hour of collection. Complete the Blood Requisition Form (Appendix K) and insert a copy of with shipment.

Supplies:

- 10 mL purple/lavender-top EDTA-containing vacutainer tubes (BD Vacutainer, Catalog no. 366643)
- clear 15ml polypropylene tubes

- 2ml cryovials
- Labels designed for low temperatures (*e.g.*, Cryo-Tag brand)

Processing:

1 Draw blood into one 10ml lavender top (K_2EDTA) tube (BD Vacutainer, Catalog no. 366643)

2 Invert tubes 10 times to mix blood

3 Centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)

4 Remove plasma from each tube and transfer equally into two separate clean 15ml polypropylene tubes

5 Repeat centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions).

6 Aliquot approximately 1.0ml of plasma from each tube into each 2.0ml cryovial. A total of 5 capped cryovials are needed for EDTA plasma.

7 Label tubes with the following information (using a Sharpie or Cryopen):

- Protocol Name
- Subject Study Number
- Subject Initials
- Sample Date and Time
- Sample Type (EDTA plasma)
- Cycle #

8 Vials should be frozen at -80ºC immediately in an upright position and kept at -80ºC until shipment.

9 As plasma samples are analyzed in a retrospective manner, samples should be stored at the other sites outside Yale and shipped in batches at a later time to be agreed with the analyzing laboratory.

10 Complete the Plasma Biomarker Sample Shipping Form (Angiogenesis and Inflammation Markers) (Appendix K) and insert a copy of with shipment.

D. Blood for Angiome Shipment:

Instructions for packing and notifications for shipment follow:

- Agree to the timing of shipment with receiving laboratory.
- Use at least 5 kg dry ice for overnight delivery. The amount of dry ice may have to be increased if a large number of samples are sent or for a large shipping container.
- Samples should be placed upright in cryoboxes containing inserts.
- Include a completed Plasma Biomarker Sample Shipping Form for Markers of Angiogenesis and Inflammation (see Form 3) itemizing the

contents of the shipment. A photocopy should be maintained with study records at each site.

- Place any paperwork in a plastic Ziploc bag.
- Send an email notification to the receiving lab with tracking number, and attach electronic version of completed Biomarker Sample Shipping Form to andrew.nixon@duke.edu and the study coordinator (email tbd).
- All samples must be shipped on dry ice by overnight delivery Monday through Wednesday (no holidays in the same week) to the following address:

Phase I Biomarker Laboratory
Dr. Andrew Nixon
Duke University Medical Center
395 MSRB, Research Drive
Durham, NC 27710
Phone: (919) 681-2239
Email: andrew.nixon@duke.edu

APPENDIX J TISSUE REQUSITION FORM

A Randomized Phase II Trial of Olaparib and Cediranib versus Olaparib in men with Metastatic Castration Resistant Prostate Cancer

Date:		Protocol Number:	
Site Contact Name:		Phone Number:	
Fax Number:		Email Address:	
Institution:		Site PI Name:	
Patient ID:			
Imaging-Guided Biopsy			
Date of Collection:			
Collection:	□ Pre-treatment	□ On-treatment	□ Off-treatment
Site of Collection:	□ Bone	□ Liver	□ Lymph Node
	□ Other (specify)		
Tissue Specimen Information *Please complete for up to 6 cores.*			
Specimen #1:		Specimen #2:	
Time of Collection:	(HH:MM)	Time of Collection:	
Time of OCT Frozen:		Time of OCT Frozen:	
Length of core:		Length of core:	
Specimen #3:		Specimen #4:	
Time of Collection:		Time of Collection:	
Time of OCT Frozen:		Time of OCT Frozen:	
Length of core:		Length of core:	
Specimen #5:		Specimen #6:	
Time of Collection:		Time of Collection:	
Time of OCT Frozen:		Time of OCT Frozen:	
Length of core:		Length of core:	
Time transferred to -80:			
Comments/Deviations from Laboratory Manual:			

APPENDIX K BLOOD REQUISITION FORM

A Randomized Phase II Trial of Olaparib and Cediranib versus Olaparib in men with Metastatic Castration Resistant Prostate Cancer

Date:		Protocol Number:	
Site Contact Name:		Phone Number:	
Fax Number:		Email Address:	
Institution:		Site PI Name:	
Patient ID:			
Date of Collection:		Time of Collection:	(HH:MM)
Whole Blood for Germline DNA/RNA □			
Whole Blood:	Specimen ID:		# of Vials:
	Time Frozen:		(HH:MM)
Blood for Angiome □			
Blood Specimen ID:			# of Vials:
Time Frozen:			(HH:MM)
Comments/Deviations from Laboratory Manual:			

APPENDIX L RESEARCH LAB DATA TABLE

	Day-6 to 0	C1 Day 1	C 1 Week 4	Day 1 Subseq. cycles	Off-Treatment Visit	Shipping Frequency/Type	Shipping Destination
Tissue Specimens							
Metastatic Biopsy	X[1]		X[1]		X[1]	Same-Day, 24-hour Ship, Dry Ice (-80°)	Lank Center for GU Oncology at DFCI (→ University of Washington, The Broad Institute)
Blood Specimens							
Germline DNA	X					Same-Day, 24-hour Ship, Dry Ice (-80°), with Biopsy Sample	Lank Center for GU Oncology at DFCI (→ University of Washington, The Broad Institute)
Angiome		X[2]		X	X		Duke University

[1]: Biopsy tissue prioritization: (in the order of importance)

a. **BROCA-HR panel (UW)**
b. **WES & WTS (Broad)**

[2]: baseline; to be collected before taking the first dose of study drugs.