Summary of Changes - Protocol

NCI Protocol #: 9881
Local Protocol #: 1604017576
Protocol Version Date: September 7, 2021
Informed Consent Version Date: September 7, 2021

Protocol Title:
NCI# 9881: A Phase 2 Study of Cediranib in Combination with Olaparib in Advanced Solid Tumors.

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 **69**
		• 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.	TOC	Table of Contents updated.

NCI Protocol #: 9881

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ClinicalTrials.gov Identifier: NCT02498613

TITLE: A Phase 2 Study of Cediranib in Combination with Olaparib in Advanced Solid Tumors

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

IND #:

IND Sponsor: DCTD, NCI

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Amendment / Version 5 / June 5, 2017
Amendment / Version 6 / September 28, 2017
Amendment / Version 7 / March 26, 2018
Amendment / Version 8 / May 16, 2018
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Amendment / Version 14 / September 7, 2021

SCHEMA

This is an open-label, multi-disease cohort, phase II study of cediranib plus olaparib for patients with advanced solid tumors. The study has a Simon 2-stage design to assess anti-tumor activity of the combination therapy in each of the disease cohorts running in parallel. These cohorts include:

(a) Non-small cell lung cancer (NSCLC)
(b) triple-negative breast cancer (TNBC)
(c) pancreatic ductal adenocarcinoma (PDAC) and
(d) small cell lung carcinoma (SCLC).

The primary endpoint is the objective response rate in each of the cohorts, as defined by RECIST version 1.1. The secondary endpoints are safety and tolerability and progression free survival in each of these cohorts.

As shown in the **Figure 1** below, patients in each cohort will be treated with cediranib monotherapy followed by the combinatorial therapy. During the cediranib monotherapy lead-in, several correlative studies will be performed, including FMISO-PET/CT scans, a tumor biopsy, serum angiogenesis markers and plasma circulating tumor DNA (ctDNA). Additional serum angiogenesis markers and plasma ctDNA will be collected throughout the study.

FMISO-PET/CT will be performed in 6 evaluable patients with NSCLC at minimum. FMISO-PET/CT scans are not required for other disease cohorts.

One baseline tumor biopsy is required for all study patients for a BROCA test. This biopsy may be waived if a patient has a tumor biopsy sample collected within the past 3 months and has not received any systemic anti-cancer therapy in the interim.

Serum angiogenesis markers and plasma ctDNA will be required in all patients.

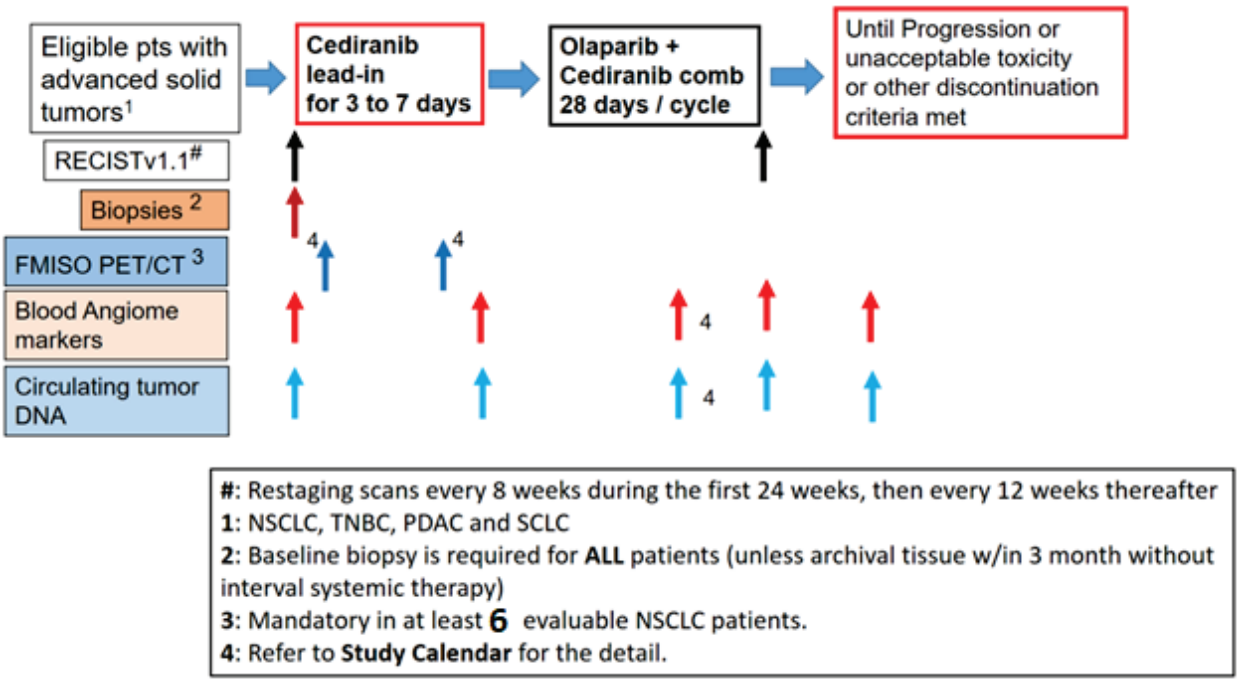


Figure 1. Study Schema

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the objective response rate (ORR) of cediranib plus olaparib in combination in patients with advanced or metastatic solid tumors of the following tumor types: non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), pancreatic ductal adenocarcinoma (PDAC), and small cell lung cancer (SCLC). The responses will be assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

1.2 Secondary Objectives

1.2.1 To assess the safety and tolerability of oral administration of cediranib in combination with olaparib in patients with select advanced solid tumors.

1.2.2 To estimate progression free survival (PFS) in each tumor cohort

1.3 Exploratory Objectives

1.3.1 To estimate the prevalence of the mutations of DNA repair genes in tumors using the BROCA panel and to correlate tumor regression with mutations status **(Integrated)**

1.3.2 To evaluate changes in tumor hypoxia on cediranib treatment compared to baseline by [F-18] fluoromisonidazole (FMISO) PET/CT in patients with NSCLC.

1.3.3 To evaluate levels of angiogenesis/ inflammatory markers including VEGF at baseline and on treatment

1.3.4 To evaluate levels of ctDNA at baseline and on treatment.

2. BACKGROUND

2.1 Study Diseases

Malignancies of lung, breast, prostate and pancreas are among the top 4 lethal cancers in the U.S., accounting for 50% of all cancer-related death in men and 48% in women. Despite recent advances in molecularly targeted therapies in lung and breast cancers, the benefits of these therapies are limited to a subset of patients whose tumor harbor sensitizing genetic aberrations. Treatment options for advanced NSCLC, TNBC, PDAC, and SCLC are limited when their disease progresses after first- or second-lines chemotherapies. The median overall survivals in these patients are in the range of 4 to 8 months.

2.1.1 Non-Small Cell Lung Cancer (NSCLC)

NSCLC is the leading cause of cancer related death in the US [1]. The identification of mutations in lung cancer has led to the development of molecularly targeted therapies to improve the survival of subsets of patients with metastatic disease [2].The use of combination chemotherapy has shown objective responses and small improvement in survival patients with metastatic disease [3]. Patients with good performance status and symptomatic disease are often treated with the first-line platinum-based doublet chemotherapy. Bevacizumab added to paclitaxel and carboplatin, has shown to improve median OS (12.3 vs 10.3 mos) [4], and was approved in 2006, for the first-line systemic treatment of patients with advanced non-squamous, non-small cell lung cancer.

Patients with NSCLC who have relapsed after front-line platinum-based doublet chemotherapy, can be considered for second-line therapies, such as docetaxel, pemetrexed and others. The median overall survival for these patients receiving second line chemotherapy is about 6-8 months [5-7]. In December 2014, ramucirumab, an IgG1 monoclonal antibody that targets the extracellular domain of VEGFR-2, was approved by the US FDA, based on data from a randomized phase III trial demonstrating a survival difference of 1.4 months (10.5 vs 9.1 months in docetaxel plus ramucirumab vs docetaxel alone)[8].

2.1.2 Triple-negative breast cancer (TNBC)

Triple-negative breast cancer (TNBC), characterized by the absence or minimal expression of estrogen (ER) and progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2), accounts for 15% to 20% of invasive breast cancers diagnosed in the United States. It is more common in younger women, African Americans, Hispanics, and BRCA1-mutation carriers. With no targetable characteristic molecular mutations yet identified, standard treatment for TNBC remains chemotherapy. In early-stage TNBC, recurrence-free (RFS) and overall survival (OS) are improved significantly with adjuvant chemotherapy, including dose-dense treatment [9], but overall prognosis remains inferior to that of other breast cancer subtypes, with higher risk of early relapse, often involving viscera.

The 5-year survival of patients with TNBC is less than 30%, and almost all patients will die because of the progression of their disease despite adjuvant chemotherapy [10]. Current systemic treatment options for metastatic TNBC patients are primarily represented by cytotoxic chemotherapy. Although chemotherapy remains the mainstay of treatment for metastatic TNBC, there are no standard chemotherapeutic schedules to date.

2.1.3 Pancreatic adenocarcinoma (PDAC)

Approximately, 48,960 new cases and 40,560 deaths of pancreatic cancer are estimated to occur in the United States in 2015 [1]. While it is 6th in rank in terms of incidence, it is the 4th leading cause of cancer related death in the U.S. The incidence of carcinoma of the pancreas has markedly increased over the past several decades and ranks as the fourth leading cause of cancer death in the United States. Despite the high mortality rate associated with pancreatic cancer, its etiology is poorly understood.

The front-line systemic chemotherapy options for stage IV disease include: gemcitabine-based therapies[11-13] and 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) [14]. However, the objective response rates are low, and the median survival for those undergoing the modern first line therapies remain less than a year [13, 14]. No standard second-line systemic therapy exists. The CONKO-003 trial suggested that a second line 5-FU, oxaliplatin- based combination chemotherapy after progression on a gemcitabine-based regimen may be beneficial compared with best supportive care [15]. Median survival on second-line chemotherapy was 4.82 months (95% CI, 4.29–5.35) for the OFF-regimen treatment and 2.30 months (95% CI, 1.76–2.83) with BSC alone (HR = 0.45; 95% CI, 0.24–0.83).

2.1.4 Small cell lung cancer (SCLC)

SCLC accounts for approximately 15% of bronchogenic carcinomas. Given its high tendency to proliferate and disseminate, approximately 70% of patients with SCLC present with extensive stage disease (ED), i.e., the disease outside of the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes [16]. While SCLC is more responsive to chemotherapy and radiation therapy than other cell types of lung cancer, a cure is impossible for extensive stage disease or relapsed disease. Chemotherapy for patients with ED-SCLC is commonly given as a two-drug combination of platinum and etoposide in doses associated with at least moderate toxic effects (as in limited-stage [LD] SCLC) [17]. Doses and schedules used in current programs yield overall response rates of 50% to 80% and complete response rates of 0% to 30% in patients with ED [18]. Unfortunately, the high initial responses seen with SCLC patients is short-lived, and most patients succumb to disease recurrence and progression within the first year after frontline therapy. Topotecan is the only agent with regulatory approval for treatment of relapsed SCLC. A randomized phase III study of IV topotecan vs CAV (cyclophosphamide, doxorubicin and vincristine) for relapsed SCLC showed comparable objective response rates (24.3% vs 18.3%, p=0.285) and survival, but with more favorable quality of life and symptom control with topotecan. The median overall survival for these patients was about 25 weeks [19].

Another study of oral topotecan versus best supportive care (BSC) in 141 patients with relapsed SCLC also showed the benefit of topotecan on survival (13.9 weeks to 25.9 weeks, p=0.0104) and improved quality of life and symptom control [20].

2.2 CTEP IND Agents

2.2.1 Cediranib (AZD2171)

Cediranib (AZD2171) quinazoline maleate; AZD2171 maleate) is an orally (PO) administered small molecule vascular endothelial growth factor (VEGF) receptor tyrosine kinase (TK) inhibitor with activity against all 3 VEGFRs [21-23]

Mechanism of Action

VEGF is a key angiogenic factor, and has been implicated in tumor blood vessel formation and in disease progression in a range of solid tumor malignancies (Hicklin and Ellis, 2005). Two high-affinity VEGF transmembrane receptors (VEGFRs) with associated TK activity have been identified on human vascular endothelium, VEGFR-1 (also known as fms-like tyrosine kinase 1 or Flt-1) and VEGFR-2 (also known as kinase insert domain-containing receptor or KDR) [24]. VEGFR-1 and VEGFR-2 signaling help mediate tumor progression. Cediranib has been developed as a potent inhibitor of VEGFR-1 and VEGFR-2 [22]. Cediranib also has activity against VEGFR-3 and c-Kit [23, 25]. Cediranib is expected, with chronic oral dosing, to inhibit VEGF-driven angiogenesis and as a result, prevent the progression and metastasis of solid tumors.

Nonclinical Efficacy

The effect of cediranib was studied in athymic *nu/nu* mice bearing established subcutaneous human tumor xenografts of diverse histologies [SW620 (colon), PC-3

(prostate), Calu-6 (lung), SKOV-3 (ovarian), and MDA-MB-231 (breast)]. Animals were administered cediranib PO at doses from 0.75-6 mg/kg/day (2.25-18 mg/m^2/day) in a constant volume of 0.1 mL/10 g body weight for 24-28 days. Cediranib produced a statistically significant inhibition of tumor growth in all human tumor types examined when dosed at 1.5 mg/kg/day (4.5 mg/m^2/day) or higher [22]. The broad anti-tumor activity of cediranib was confirmed alone and in combination with other anti-cancer agents in a wide range of models. Using a transgenic mouse model in which multiple mammary tumors spontaneously develop after two pregnancies, the temporal effects of cediranib administration was studied [26]. When dosed with cediranib (0.75- 6 mg/kg/day PO) at the time early lesions start to develop, the number of tumor foci was not affected, but their growth was inhibited. When tumors were well-established before cediranib was given (at doses of 3 and 6 mg/kg/day), dose-dependent growth inhibition occurred as well as tumor regression. These data are in line with inhibition of angiogenesis rather than a direct effect on tumor cells.

Nonclinical Pharmacology and Toxicology
Protein binding of cediranib (90-95%) was relatively high across all species examined and was independent of concentration (range: 0.03-10 mcg/mL) and gender (Cediranib Investigator's Brochure, 2014). Cediranib was approximately 95% bound to human plasma proteins, with human serum albumin and α_1-acid glycoprotein accounting for most of this binding.

VEGF has three major biological activities in endothelial cells of rats and primates of the age groups used in the nonclinical studies (Cediranib Investigator's Brochure, 2014). It is an important angiogenic factor, a potent physiological mediator of vascular tone (specifically of vasodilation), and a potent modulator of capillary permeability inducing endothelial cell fenestrations. VEGF receptor inhibition was therefore considered to be the cause of many of the pathophysiological changes encountered. Vascular (myocarditis, choroid plexus) and renal (glomerulosclerosis and tubular degeneration) pathologies have been seen in rat, dog, and primate dosed with cediranib which are considered to be consistent with lesions induced by hypertension, although a direct effect by cediranib on these tissues cannot be excluded. Pathological findings were also seen in the adrenal glands (degenerative cortical changes), pancreas (acinar epithelial cell necrosis), thyroid (follicular epithelial cell atrophy), liver (hepatocyte necrosis), and biliary system (cholangitis and bile duct proliferation and bile duct cholangitis) of the rat. In addition in the primate, changes were seen in the gallbladder (mucosal hypertrophy) and bile duct (hyperplasia/hypertrophy).

Cediranib did not induce rat hepatic microsomal P450 activity but caused a 40-60% reduction in CYP1A activity at the 5 mg/kg dose level (cediranib Investigator's Brochure, 2014). Inhibition studies *in vitro* using human hepatic microsomal protein gave IC_{50} values for cediranib against CYP2D6, CYP3A4 testosterone, and CYP3A4 midazolam of 32.9, 16.2, and 21.4 mcg/mL, respectively. For CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1, the IC_{50} values were outside the concentration range of cediranib examined. As the clinically relevant plasma concentration of cediranib has not yet been determined, any possible effect on compound clearance and drug interaction is currently

unknown.

Further details of the nonclinical pharmacology and toxicity of cediranib can be found in the cediranib Investigator's Brochure (2014).

Clinical Pharmacology (cediranib Investigator's Brochure 2014)
Following single and multiple oral doses, absorption is extended, with Cmax typically attained between 1 and 8 h post-dose. Although absolute bioavailability has not been determined, cediranib appears well absorbed with apparently linear PK for single and multiple doses ranging from 0.5 to 60 mg. After attaining Cmax, plasma concentrations decline in an apparent bi-exponential manner, with a t½λz of 22.0 ±6.50 h.

After multiple once-daily oral doses, steady-state plasma concentrations are attained after approximately 7 days. There is limited accumulation (<3 fold), consistent with the t½λz observed following single doses, and steady-state plasma concentrations are predicted by the single-dose PK, indicating no time-dependent changes in PK.

Cediranib binds to human plasma proteins (95.4%), including serum albumin and α1-acid glycoprotein, independent of concentration over the range 0.06 to 22 μM (30 to 1000 ng/mL).

Clearance of cediranib is moderate (CL/F, 28.2 ±15.1 L/h, mean ±SD), approximating 64% of nominal hepatic plasma flow. In patients administered 45 mg radiolabelled cediranib, the majority of the radioactive material recovered was excreted in the faeces (58.8% ±26.9) and urine (20.8% ±7.1) within 7 days. Only a small fraction (<1% of the administered dose) of cediranib was excreted unchanged in the urine.

Dose-proportional increases in Css,max and AUCss were observed for cediranib doses ranging from 0.5 to 60 mg; however, further PK data are needed to make a definitive statement about linearity or dose proportionality.

Data obtained following a single 45-mg dose in the presence and absence of a standard high-fat meal, show that food decreases Cmax by 33% and AUC by 24%. Cediranib should be administered at least 1 h before or 2 h after food.

Comparison of studies conducted in Japanese patients, with corresponding Western study data indicates similar PK between Western and Japanese patients.

Safety Profile
Hypertension is an expected AE with agents that inhibit VEGF signaling. In cediranib studies, increases in blood pressure have been observed and cases of hypertension have been reported, including CTC Grade 4 hypertension and end-organ damage related to hypertension, such as cerebrovascular events.

Left ventricular dysfunction, in some cases leading to cardiac failure, has been observed in patients receiving cediranib with risk factors for left ventricular dysfunction (including

previous or concomitant anthracycline treatment).

A number of events of bleeding and hemorrhage have occurred, they were mostly mild and the most common type of bleeding was mucocutaneous (epistaxis). However, gastrointestinal, central nervous system, pulmonary bleeding and hematuria have also been reported. Some reports of hemorrhage were fatal but causality could not be unequivocally assigned to cediranib.

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.

Pancreatitis has been infrequently reported in patients receiving cediranib.

Fatigue, hand and foot syndrome, diarrhea, headache, nausea, vomiting, anorexia and weight loss are commonly occurring AEs in cediranib studies. Dehydration has been observed in clinical studies as a consequence of cediranib-related or chemotherapy-related diarrhea, vomiting, anorexia, or reduced oral intake.

Hoarseness (dysphonia) has been reported as common and dose-related.

Muscle weakness, proteinuria, dry mouth and oral mucosal inflammation have been observed in cediranib studies. Impaired wound healing, generally low grade has been seen. Infections, generally low grade, have been reported. Arterial thromboembolism (including cerebrovascular accident, myocardial infarction and infrequent retinal arterial occlusion) and venous thromboembolic events (including pulmonary embolism and retinal vein occlusion) have been observed in patients receiving cediranib.

Recommended Dose:
Based on the totality of the safety, tolerability, efficacy, PK, and pharmacodynamic data that are currently available from both AZ-sponsored and collaborative group studies with cediranib, the following general recommendations regarding cediranib doses in clinical studies have been made:
• Cediranib 30 mg is the recommended dose for monotherapy.
• Cediranib 20 mg is the recommended dose in combination with chemotherapy agents.

Clinical Experience
The following summarizes a few key clinical trials of cediranib in the diseases that are being studied:

1. **NSCLC**
A phase I and pharmacokinetic study of daily oral cediranib in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer was led by the National Cancer Institute of Canada Clinical Trials Group [27]. Patients received cisplatin 80 mg/m2 on day 1 and gemcitabine 1250 mg/m2 on days 1 and 8 of a 3-week cycle, and daily oral cediranib at either 30 mg or 45 mg. Fifteen patients were enrolled. No dose-

limiting toxicities were observed during cycle 1. Fatigue, nausea, diarrhea, anorexia and granulocytopenia were common; hypertension was manageable. No grade 3/4 bleeding occurred. At 45 mg/d, fatigue, diarrhea and thrombocytopenia were increased; and headache, hoarseness and grade 2 hand-foot syndrome were observed. Cediranib had no effect on cisplatin elimination, but clearance of gemcitabine is significantly reduced in the presence of cediranib ($p>0.02$). Central review confirmed responses in four of 15 enrolled patients (26.7%, 95% CI 7.8-55%) and four of 12 evaluable patients (33.3%, 95% CI 9.9-65%). It was concluded that cediranib at 30 mg daily could be combined with standard doses of cisplatin/gemcitabine with encouraging anti-tumor activity, and was the recommended phase III dose. Toxicity was higher, but was deemed predictable and manageable.

The NCIC clinical trials group led another phase I pharmacokinetic study of daily oral AZD2171 in combination with carboplatin and paclitaxel in patients with advanced non-small-cell lung cancer [28]. Patients received carboplatin targeted to an area under the concentration time curve of 6 and paclitaxel 200 mg/m^2, both on day 1 of a 3-week cycle; daily oral AZD2171 at either 30 mg or 45 mg commenced day 2 of cycle 1. Twenty patients were enrolled. No dose-limiting toxicities were observed during cycle 1 at either dose. Fatigue, diarrhea, anorexia, and granulocytopenia were common; hypertension was manageable with a treatment algorithm designed for this protocol. No clinically significant drug-related bleeding was observed. At 45 mg/d, fatigue and diarrhea were increased, and headache and hoarseness were observed. Paclitaxel clearance decreased during cycle 2, but no other significant pharmacokinetic interactions were observed. After radiology review, confirmed responses were observed in nine patients (response rate, 45%; 95% CI, 23% to 68%); all but one enrolled patient showed evidence of tumor shrinkage, some with cavitation. Based on this data, a larger Phase II/III, BR24 study was undertaken.

The BR24 study was a phase II/III double-blind study to assess efficacy and safety of cediranib at 30mg with standard chemotherapy as initial therapy for advanced non-small-cell lung cancer (NSCLC) [29]. Paclitaxel (200 mg/ mg/m^2) and carboplatin (area under the serum concentration-time curve 6) were given every 3 weeks, with daily oral cediranib or placebo at 30 mg (first 45 patients received 45 mg). Progression-free survival (PFS) was the primary outcome of the phase II interim analysis. A total of 296 patients were enrolled, 251 to the 30-mg cohort. The phase II interim analysis demonstrated a significantly higher response rate (RR) for cediranib than for placebo, HR of 0.77 for PFS, no excess hemoptysis, and a similar number of deaths in each arm. The study was halted to review imbalances in assigned causes of death. Approximately 13% of the deaths in the cediranib group was deemed related to protocol toxicity +/- NSCLC vs 0% protocol toxicity related death in the placebo. In the primary phase II analysis (30-mg cohort), the adjusted HR for PFS was 0.77 (95% CI, 0.56 to 1.08) with a higher RR for cediranib than for placebo (38% v 16%; $P < .0001$). Cediranib patients had more hypertension, hypothyroidism, hand-foot syndrome, and GI toxicity. Hypoalbuminemia, age > or = 65 years, and female sex predicted increased toxicity. Survival update ($N = 296$) 10 months after study unblinding favored cediranib over placebo (median of 10.5 months v 10.1 months; HR, 0.78; 95% CI, 0.57 to 1.06; $P = .11$). Subsequently, it led to the BR29 study, randomized, double-blind, placebo-controlled trial of cediranib 20 mg with carboplatin and paclitaxel in advanced

NSCLC.

The BR29 study was a randomized double-blind placebo-controlled study to evaluate the addition of cediranib 20mg to standard carboplatin/paclitaxel chemotherapy in advanced non-small cell lung cancer [30]. Eligible patients received paclitaxel (200mg/m2 and carboplatin (area under the concentration time curve 6) intravenously every 3 weeks. Daily oral cediranib/placebo 20mg was commenced day 1 of cycle 1 and continued as monotherapy after completion of 4-6 cycles of chemotherapy. The primary end-point of the study was overall survival (OS). The trial would continue to full accrual if an interim analysis (IA) for PFS, performed after 170 events of progression or death in the first 260 randomized patients, revealed a hazard ratio (HR) for PFS of $\leqslant 0.70$. The trial was halted for futility at the IA (HR for PFS 0.89, 95% confidence interval [CI] 0.66-1.20, p = 0.45). A final analysis was performed on all 306 enrolled patients. The addition of cediranib increased response rate ([RR] 52% versus 34%, p = 0.001) but did not significantly improve PFS (HR 0.91, 95% CI 0.71-1.18, p = 0.49) or OS (HR 0.94, 95% CI 0.69-1.30, p=0.72). Cediranib patients had more grade 3 hypertension, diarrhea and anorexia. It was concluded that the addition of cediranib 20mg daily to carboplatin/paclitaxel chemotherapy increased RR and toxicity, but not survival.

The North Central Cancer Treatment Group Study led another randomized phase II study of gemcitabine and carboplatin with or without cediranib as first-line therapy in advanced non-small-cell lung cancer (N0528) [31]. This study was to assess the safety and efficacy of gemcitabine and carboplatin with (arm A) or without (arm B) daily oral cediranib as first-line therapy for advanced non-small-cell lung cancer. A lead-in phase to determine the tolerability of gemcitabine 1000 mg/m on days 1 and 8, and carboplatin on day 1 at area under curve 5 administered every 21 days with cediranib 45 mg once daily was followed by a 2 (A):1 (B) randomized phase II study. The primary end point was confirmed overall response rate (ORR) with 6-month PFS (PFS6) rate in arm A as secondary end point. On the basis of the safety assessment, cediranib 30 mg daily was used in the phase II portion. A total of 58 and 29 evaluable patients were accrued to arms A and B. Patients in A experienced more grade 3+ nonhematologic adverse events, 71% versus 45% (p = 0.01). The ORR was 19% (A) versus 20% (B) (p = 1.0). PFS6 in A was 48% (95% confidence interval: 35%-62%), thus meeting the protocol-specified threshold of at least 40%. The median overall survival was 12.0 versus 9.9 months (p = 0.10).

2. Triple Negative Breast Cancer (TNBC)

A phase I trial of olaparib plus cediranib enrolled patients with triple negative breast cancer or with recurrent epithelial ovarian cancer. Twenty-eight patients (20 ovarian, 8 breast) enrolled to 4 dose levels. Two dose limiting toxicities (DLTs) (1 grade 4 neutropenia ≥ 4 days; 1 grade 4 thrombocytopenia) occurred at the highest dose level (cediranib 30 mg daily; olaparib 400 mg twice daily [BID]). The RP2D was cediranib 30 mg daily and olaparib 200 mg BID. Grade 3 or higher toxicities occurred in 75% of patients, and included grade 3 hypertension (25%) and grade 3 fatigue (18%). One grade 3 bowel obstruction occurred. The overall response rate (ORR) in the 18 RECIST-evaluable ovarian cancer patients was 44%, with a clinical benefit rate (ORR plus stable disease (SD) > 24 weeks) of 61%. None of the seven evaluable breast cancer patients achieved clinical

response; two patients had stable disease for > 24 weeks.

3. PDAC

Cediranib has not been tested in patients with pancreatic cancer.

4. SCLC

NCI #7097 was a phase II trial of cediranib (AZD2171) for second-line therapy of small cell lung cancer [32]. The dose of cediranib was 45 mg PO once a day for the first 12 patients and was reduced to 30 mg PO once a day for the subsequent patients because of intolerance of the higher dose. Treatment was given on a daily continuous schedule. The primary end point was determination of the response rate. Twenty-five eligible patients were enrolled. A median of two cycles were administered. Salient grade 3/4 toxicities were fatigue, diarrhea, hypertension, proteinuria, and elevated liver enzymes. Tolerability was better with the 30 mg dose once a day. Nine patients had stable disease, but no patient had a confirmed PR. The median PFS and OS were 2 and 6 months, respectively. Response criteria to proceed to full accrual were not met.

Another study assessed cediranib plus EP as first-line therapy for extensive stage/metastatic lung cancer [33]. Pts received up to six 21-day cycles of EP (E 100 mg/m^2, days 1-3; P 80 mg/m^2, day 1) with once-daily cediranib from day 4 of cycle 1 until disease progression or toxicity and were eligible for safety review if they completed the first 21 days of cediranib or had a dose limiting toxicity (DLT). The primary objective was assessment of safety and tolerability. At data cut-off, 22 pts had received treatment. Recruitment to the 30 mg cohort was stopped at 4 pts (all SCLC) when 20 mg became the recommended dose with chemotherapy. As only 1/6 pts in the initial cediranib 20 mg cohort experienced a DLT (hemoptysis), this combination was considered suitable for cohort expansion. Adverse events (AEs) reported in ≥ 50% pts receiving cediranib 20 mg + EP were nausea, vomiting, neutropenia and diarrhea. The incidences of hypertension and fatigue were both 39%. Five pts discontinued treatment due to an AE: anemia, duodenal ulcer bleeding, increased creatinine and hemoptysis. In a preliminary efficacy assessment (RECIST), 10/14 (71%) SCLC pts achieved a partial response (PR) (12/18 [67%] including 30 mg cohort). In the 20 mg cohort, the mean best change from baseline in tumor size was -53.3%. Median PFS was 8 months and 5/8 ongoing pts had a PR. Cediranib 20 mg + EP was well tolerated and has shown evidence of activity in SCLC and lung NEC

2.2.2 **Olaparib (AZD2281; Lynparza™)**

Olaparib (AZD2281, KU-0059436) is a potent oral inhibitor of PARP-1 and PARP-2. PARP inhibition is a novel approach to targeting tumours that have homologous recombination deoxyribonucleic acid (DNA) repair (HRR) pathway deficiencies (HRD). In HRD tumours, single agent treatment with olaparib can lead to tumour regression by a process known as synthetic lethality- a result of the accumulation of un-repaired DNA double-strand breaks (DSBs) and an unsupportable increase in genomic instability.

Olaparib is the first PARP inhibitor approved by regulatory agencies for clinical indication. US Food and Drug Administration (FDA) approved its use for a monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated, advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The European Medicines Agency approved its use as a 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.

Mechanism of Action
Preclinically, olaparib displays antitumor activity against a variety of tumor cell lines and this sensitivity of the cells is believed to depend upon components of a defective HRR capability (Olaparib Investigator's Brochure, 2014). As a major example of this selective activity, both BRCA1- and 2-deficient (-/-) tumors are sensitive to PARP inhibition. Early studies indicated that PARP inhibition in BRCA1/2 homozygous null cells, but not the isogenic BRCA heterozygous cells, led to cell death. BRCA1 and 2 are proteins necessary for proper function of HRR, the high fidelity repair system that addresses DNA double-strand breaks (DSBs). The backup repair system to HRR is base-excision repair (BER), which requires PARP function and primarily addresses single-strand breaks (SSBs). However, the system works both ways in that repair of SSBs in BER can lead to stalled replication forks that strain the system and cause double strand breaks, resulting in a situation that requires intact HRR and BRCA1 or BRCA2. Thus, HRR dysfunction sensitizes cells to PARP inhibition leading to further chromosomal instability, cell cycle arrest and apoptosis [34]. This sensitivity is suggested to result in a large therapeutic window for PARP inhibition in mutation carriers. Pre-clinical studies support these findings showing that other BRCA mutant, but not wild-type, human cell lines are highly sensitive to olaparib [35].

Nonclinical Pharmacology and Efficacy
Olaparib has demonstrated cellular activity in the low nM range with a cellular dose for 50% inhibition (IC_{50}) of 2 nM in HeLa cells (Olaparib Investigator's Brochure, 2014). The effective concentration for inhibiting cellular PARP activity in cancer cells by >90% is approximately 30 nM to 100 nM olaparib in several tumor cell lines including ovarian A2780, breast MCF-7, and colorectal SW620. These concentrations led to significant ablation of PARP activity (based on the inhibition of PAR formation), with maximal PARP-1 inhibition occurring at around 100 nM. Consistent with this, maximal potentiation of an appropriate DNA SSB-inducing chemotoxic agent (MMS) was also seen *in vitro* at

100 nM, which equates to 43.4 ng/mL.

Following single oral doses, absorption was rapid (maximum plasma concentration [C_{max}] <2 hours in mice, rats and dogs) while bioavailability was <60% in male and female mice, <20% in male and female rats and ~79% in male dogs (Olaparib Investigator's Brochure, 2013). Low oral bioavailability in rat may have been due to poor absorption or rapid first pass metabolism. Distribution of olaparib is in the gastrointestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Further investigations are still ongoing. Excretion is primarily via the feces and, to a lesser extent, the urine.

Investigations in human *in vitro* systems indicated metabolism of olaparib was CYP mediated and that CYP3A4 and 3A5 were the dominant metabolic enzymes (Olaparib Investigator's Brochure, 2013). Similar studies indicated flavin mono-oxygenase-3 was not able to metabolize olaparib. In *in vitro* direct inhibition assays, olaparib (100 μM) had only limited effect against CYP3A (up to 46% inhibition) and less effect against other CYPs tested. In time dependent inhibition assays, olaparib had only very minor effects against CYP3A and no effect against other CYPs. Clinically significant direct inhibition of intestinal CYP3A is possible but significant effects against hepatic CYP3A are less likely. The CYP induction potential of olaparib was investigated in cultures of human hepatocytes. At the highest olaparib concentration (30 microM), minor induction of CYP2B6 activity was observed (<40% positive control) and smaller effects on CYPs 2C9 and 2C19 activities were noted. These changes were unlikely to be of clinical significance. A small decrease in CYP3A activity was noted, which may suggest time-dependent inhibition, however, this was not explored further.

In studies using Madin-Darby Canine Kidney (MDCK) II cells transfected with multidrug resistance 1 (MDR1; Pgp), BCRP or MRP-2 drug efflux transporters, olaparib was shown to be a substrate of MDR1 but not BCRP or MRP-2 (Olaparib Investigator's Brochure, 2013). In the same systems, olaparib was an inhibitor of BCRP and MRP-2 but had little or no inhibitory effect on MDR1.

In isolated human hepatocytes, olaparib was a substrate for organic anion transport proteins. In the same system, olaparib was shown to be an organic cation transporter 1 (OCT1) inhibitor (IC_{50} 11.9 μM) (Olaparib Investigator's Brochure, 2013). In HEK-293 cells transfected with OATP1B1, olaparib functioned as an inhibitor and IC_{50} values of 20.3 microM and 27.1 microM were derived (substrate dependent). Using the criteria defined in the European Medicines Agency (EMA) guidelines on the investigations of drug interactions (EMA 2013), it is possible olaparib may precipitate an interaction via hepatic drug uptake transporters, particularly OCT1.

SimCYP population PK simulations of the separate effect of co-administration of itraconazole and rifampicin (clinically relevant CYP3A inhibitor and inducer, respectively) on olaparib PK in humans, when administered at the recommended human dose, were performed (Olaparib Investigator's Brochure, 2013). The itraconazole (200 mg twice daily [BID] x 7 days) simulation indicated olaparib (400 mg bd x 7 days) steady state C_{max} and

area under the concentration-time curve (AUC) would increase by 2.8 and 3.5 fold, respectively. The rifampicin simulation (600 mg x 6 days) indicated olaparib (400 mg BID x 6 days) steady state C_{max} and AUC in the presence of rifampicin would be reduced to 33% and 29%, respectively, of the values in the absence of rifampicin.

Nonclinical Toxicology
Olaparib has been tested in dogs and rats (Olaparib Investigator's Brochure, 2013). There were no noted effects on the cardiovascular or respiratory parameters of an anesthesized dog or any behavioral, autonomic, or motor effects in the rat. Toxicology studies indicate that the target organ of toxicity is the bone marrow. *Ex vivo* work has confirmed that olaparib is also active against human marrow. The cytotoxic effect becomes evident at a higher concentration than required to fully ablate PARP activity. 28-day dog and rat studies demonstrate a reversible myelotoxic effect that is mild to moderate. Platelets are first affected, followed by white blood cells. In 26-week repeat-dose studies in rats, doses were well-tolerated in male rats, with hematological effects and increased spleen weights observed at all dosages. In female rats, doses of 15 mg/kg/day resulted in significant reduction in body weight. Hematological effects and increased spleen weights were again observed at all dosages. The difference between sexes was considered to be due to the fact that females had greater plasma exposure levels than males. In 26-week repeat-dose studies in dogs, olaparib was well-tolerated. Hematological changes were observed, characterized by pancytopenia.

Clinical Pharmacology- Single dose Tablet Data (Olaparib Investigator's Brochure, 2014)

Following administration of single oral doses of the tablet formulation at doses of 25, 50 and 250 mg (n=6 per cohort), absorption was rapid and slightly more rapid than seen following the capsule dose. The Cmax was typically achieved between 0.5 hours and 2 hours after dosing. Following the peak, plasma concentrations declined biphasically with a terminal t½, across all 3 dose levels, of between 5 hours and 9 hours (average=6.97 hours±1.06 Sd). Both Gmean Cmax and AUC increased approximately proportionally with dose (8-fold and 12-fold, respectively, for a 10-fold increase in dose). The mean volume of distribution of olaparib was 54.9 L±30.1 Sd and the mean plasma clearance was 5.42 L/h±2.60 Sd.

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

Table 1.2.1.3-1. Systemic Exposure of Olaparib Tablet vs. Capsule Formulations			
Parameter	**25 mg tablet vs. 50**	**50 mg tablet vs. 100**	**250 mg tablet vs.**

	mg capsule	mg capsule	400 mg capsule
C_{max} ratio	1.29	1.53	2.49
90% CI	1.10, 1.52	1.11, 2.11	1.87, 3.31
AUC ratio	1.03	0.99	1.74
90% CI	0.85, 1.24	0.69, 1.42	1.36, 2.23

C_{max} = maximum plasma concentration, AUC = area under the concentration-time curve, CI = confidence interval

Safety Profile: As of 02 October 2013, approximately 2103 patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumors are estimated to have received treatment with olaparib across the dose range 10 mg od to 600 mg bd in AstraZeneca-sponsored, investigator-sponsored and collaborative group studies. Olaparib has been given as either monotherapy (18 studies, an estimated 1214 patients) or in combination with other
chemotherapy/anti-cancer agents (25 studies, an estimated 889 patients). Many of these combinations studies are ongoing. The majority of patients to date have received the capsule formulation of olaparib (an estimated 1635 patients). Approximately 468 patients have received the tablet formulation to date. Approximately 304 patients have received comparator or placebo across the olaparib development program.

Data from these studies indicate that olaparib is generally well tolerated at monotherapy doses up to 400 mg bd (capsule formulation) and 300 mg bd (tablet formulation) in patients with solid tumours. Administration of olaparib monotherapy has been associated with reports of laboratory findings and/or clinical diagnoses of:

- Hematological toxicity:
  - Anemia, generally mild or moderate (CTCAE Grade 1 or 2)
  - Neutropenia, predominantly mild or moderate (CTCAE Grade 1 or 2)
  - Lymphopenia, generally mild or moderate (CTCAE Grade 1 or 2)
  - Thrombocytopenia, generally mild or moderate (CTCAE Grade 1 or 2)
  - Mean corpuscular volume elevation
  - Increase in blood creatinine, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Nausea and vomiting, generally mild or moderate (CTCAE Grade 1 or 2), intermittent and manageable on continued treatment
- Decreased appetite, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Diarrhea, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Dyspepsia and upper abdominal pain, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Stomatitis, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Dysgeusia, generally mild or moderate intensity (CTCAE Grade 1 or 2)

- Fatigue, (including asthenia), generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Headache, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Dizziness, generally mild or moderate intensity (CTCAE Grade 1 or 2)

Important potential risks
MDS/AML have been reported in <1% of patients. The cases were typical of secondary MDS/therapy-related AML. The duration of therapy with olaparib in patients who developed secondary MDS/AML varied from <6 months to >2 years. All patients had potential contributing factors for the development of MDS/AML, having received extensive previous chemotherapy with platinum agents. Many had also received other DNA damaging agents.

In the ovarian study, one patient who developed MDS had had two prior lines of therapy, and had been on combination cediranib/olaparib for ~1 year when she was diagnosed with MDS.

Pneumonitis events have been reported in <1% of patients receiving olaparib (Investigator's Brochure 2014. Section 5.2.7.1). The reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy).

New primary malignancies have been reported in a small number of patients (Investigator's Brochure 2014 Section 5.2.7.1). There were other contributing factors/potential alternative explanations for the development of the new primary
malignancy in all cases.

Laboratory toxicities:
From the completed studies, there are no safety concerns noted for the renal or hepatic parameters measured and no clinically significant changes of concern relating to coagulation parameters. Changes observed in the hematological parameters (decreased hemoglobin, neutrophils, thrombocytes and lymphocytes) are known to be associated with olaparib monotherapy and/or can be explained by co-existing conditions/previous chemotherapy. Mean corpuscular volume increases have also been observed with olaparib. The clinical significance of this laboratory finding is unknown. Data from Phase I and Phase II studies of olaparib in combination with various chemotherapy agents indicate an increase in neutropenia, thrombocytopenia and anemia compared to giving these agents alone. These findings are consistent with pre-clinical findings and are reflected in the more severe hematological events i.e., CTCAE Grade 4 neutropenia, febrile neutropenia and thrombocytopenia being reported as SAEs.

Mild elevations in creatinine with no apparent sequelae have been observed in the absence of an elevation in urea or blood urea nitrogen or a reported abnormality on urinalysis. The clinical significance of these mild elevations in creatinine is unknown but inhibition of

organic cation-transporter-2 by olaparib is considered a plausible mechanistic explanation.

Clinical Efficacy:
The regulatory approvals of olaparib were based on the study D0810C00019 (versus placebo in platinum sensitive serous ovarian cancer). This is a Phase II, randomized, double blind, multicenter study to assess the efficacy of olaparib (capsule formulation) in the treatment of patients with platinum sensitive serous ovarian cancer, following treatment with 2 or more platinum containing regimens [36]. Patients were randomly assigned to receive olaparib, at a dose of 400 mg twice daily, or placebo. The primary end point was progression-free survival according to the Response Evaluation Criteria in Solid Tumors guidelines. Of 265 patients who underwent randomization, 136 were assigned to the olaparib group and 129 to the placebo group. Progression-free survival was significantly longer with olaparib than with placebo (median, 8.4 months vs. 4.8 months from randomization on completion of chemotherapy; hazard ratio for progression or death, 0.35; 95% confidence interval [CI], 0.25 to 0.49; P<0.001). Subgroup analyses of progression-free survival showed that, regardless of subgroup, patients in the olaparib group had a lower risk of progression. The investigators concluded that olaparib as maintenance treatment significantly improved progression-free survival among patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer. Interim analysis showed no overall survival benefit. The toxicity profile of olaparib in this population was consistent with that in previous studies.

Fong et al reported the result of a phase I study in a study population enriched in carriers of a BRCA1 or BRCA2 mutation [37]. The investigators enrolled and treated 60 patients; 22 were carriers of a BRCA1 or BRCA2 mutation and 1 had a strong family history of BRCA-associated cancer but declined to undergo mutational testing. The olaparib dose and schedule were increased from 10 mg daily for 2 of every 3 weeks to 600 mg twice daily continuously. Reversible dose-limiting toxicity was seen in one of eight patients receiving 400 mg twice daily (grade 3 mood alteration and fatigue) and two of five patients receiving 600 mg twice daily (grade 4 thrombocytopenia and grade 3 somnolence). This led to enrolment of another cohort, consisting only of carriers of a BRCA1 or BRCA2 mutation, to receive olaparib at a dose of 200 mg twice daily. Other adverse effects included mild gastrointestinal symptoms. There was no obvious increase in adverse effects seen in the mutation carriers. Pharmacokinetic data indicated rapid absorption and elimination; pharmacodynamic studies confirmed PARP inhibition in surrogate samples (of peripheral-blood mononuclear cells and plucked eyebrow-hair follicles) and tumor tissue. Objective antitumor activity was reported only in mutation carriers, all of whom had ovarian, breast, or prostate cancer and had received multiple treatment regimens.

In an expansion phase in BRCA-deficient ovarian cancer at a dose of olaparib 200 mg BID, fifty patients were treated, including 48 with BRCA-deficient germline mutations and two patients of unknown status or significance. Twenty (40%) patients achieved complete response (CR) or partial response (PR) by RECIST and/or GCIG-CA125 criteria. An additional three patients experienced stable disease (SD) for more than four cycles [38]. A multicenter phase 2 study enrolled two sequential cohorts of women with known germline BRCA2 or BRCA2 mutations and recurrent advanced ovarian cancer to receive

olaparib continuously at a dose of 400 mg BID (Cohort 1) or 100 mg BID (Cohort 2) [39]. Responses were observed in 33% (11 of 33) patients enrolled in the 400mg BID cohort and 13% (3 of 24) patients enrolled in the 100 mg BID cohort. A phase 2 study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer showed ORR of 41% in ovarian patients with BRCA1 or BRCA2 mutations and 24% without mutations and no confirmed responses in patients with breast cancer [40].

Kaufman et al reported the results from the phase 2 multiple phase 2 study of olaparib monotherapy in patients with advanced solid cancer and a germline *BRCA1/2* mutation[41]. Olaparib was given 400mg twice a day and the primary endpoint was tumor response rate. A total of 298 patients received treatment and were evaluable. The tumor response rate was 26.2% (78 of 298; 95% CI, 21.3 to 31.6) overall and 31.1% (60 of 193; 95% CI, 24.6 to 38.1), 12.9% (eight of 62; 95% CI, 5.7 to 23.9), 21.7% (five of 23; 95% CI, 7.5 to 43.7), and 50.0% (four of eight; 95% CI, 15.7 to 84.3) in ovarian, breast, pancreatic, and prostate cancers, respectively. Stable disease ≥ 8 weeks was observed in 42% of patients (95% CI, 36.0 to 47.4), including 40% (95% CI, 33.4 to 47.7), 47% (95% CI, 34.0 to 59.9), 35% (95% CI, 16.4 to 57.3), and 25% (95% CI, 3.2 to 65.1) of those with ovarian, breast, pancreatic, or prostate cancer, respectively.

Lee and Kohn and colleagues have examined olaparib with carboplatin in two schedules in BRCA1/2 mutation carriers with breast and/or ovarian cancer and women with high grade serous ovarian cancers [42]. They also see activity with over 80% of ovarian cancer patients attaining either SD or PR lasting up to 18+ months. Additional phase 1 and 2 trials in both BRCA-deficient and BRCA-competent ovarian cancer are currently ongoing.

2.2.3 FMISO

[1H-1-(3-[^{18}F]-fluoro-2-hydroxy-propyl)-2-nitro-imidazole, or [^{18}F]-fluoromisonidazole has a molecular weight of 189.14 Daltons. [^{18}F]FMISO is an azomycin-based hypoxic cell sensitizer that has a nearly ideal partition coefficient and, when reduced by hypoxia, binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration, rather than by any downstream biochemical interactions. The covalent binding of nitroimidazoles is due to bioreductive alkylation based on reduction of the molecule through a series of 1-electron steps in the absence of oxygen. Products of the hydroxylamine, the 2-electron reduction product, bind stably in cells to macromolecules such as DNA, RNA, and proteins. In the presence of oxygen, a futile cycle results in which the first 1-electron reduction product, the nitro radical anion, is re-oxidized to the parent nitroimidazole, with simultaneous production of an oxygen radical anion. FMISO is not trapped in necrotic tissue because mitochondrial electron transport is absent. The normal route of elimination for FMISO is renal. The LD50's in adult male Balb/C mice for MISO and FMISO are 1.8 mg/g (1.3-2.6) and 0.9 mg/g, respective. Clinical studies employing multiple dosing of MISO have also been reported and peripheral neuropathy (PN) was the manifestation of toxicity that became dose limiting with daily doses of 3-5 g/m2. ely.]

Toxicity of FMISO in Humans:

FMISO's primary toxicity is likely to be peripheral neuropathy, which is dependent upon frequency and dose level. There is no evidence to suggest that FMISO poses a risk for PN when administered as an imaging agent for PET as described herein. The risk for PN in fact appears to be minimized or absent even at therapeutic doses that far exceed those necessary for PET imaging. The maximum dose to humans reported in imaging protocols was 1 mg/kg or 70 mg for a 70 kg subject; no adverse events have been reported. This is about 0.1% of the projected LD_{50}. Total patient imaging doses of the current radiopharmaceutical formulation contain ≤ 15 µg of fluoromisonidazole and less than 35 µg of other nitroimidazole derivatives. This is <0.001% of the projected LD50. The drug is the only active ingredient and it is formulated in ≤ 10 mL of 5% ethanol in saline for intravenous injection

Table: Radiation Absorbed Dose to Organs

Tissue	Mean (mGy/MBq)	Mean (mrad/mCi)	Total / 7 mCi (mrad)
adrenals	0.0166	61.4	430
brain	0.0086	31.8	223
breasts	0.0123	45.5	319
gall bladder wall	0.0148	54.8	383
lower large intestine	0.0143	52.9	370
small intestine	0.0132	48.8	342
stomach	0.0126	46.6	326
upper large intestine	0.0140	51.8	363
heart wall	0.0185	68.5	479
kidneys	0.0157	58.1	407
liver	0.0183	67.7	474
lungs	0.0099	36.6	256
muscle	0.0142	52.5	368
ovaries	0.0176	65.1	456
pancreas	0.0179	66.2	464
red marrow	0.0109	40.3	282
bone surface	0.0077	28.5	199
skin	0.0048	17.8	124
spleen	0.0163	60.3	422
testes	0.0146	54.0	378
thymus	0.0155	57.4	401
thyroid	0.0151	55.9	391
urinary bladder wall	0.0210	77.7	544
uterus	0.0183	67.7	474
eye lens	0.0154	57.0	399
Total body	0.0126	46.6	325

Calculated total body dose for a 70 kg man injected with 3.7 MBq/kg was 0.013 mGy/MBq; for a 57 Kg woman it was 0.016 mGy/MBq. Effective dose equivalents were 0.013 mSv/MBq for men and 0.014 mSv/MBq for women. The radiation exposure from [^{18}F]FMISO is equal to or lower than that of other widely used nuclear medicine studies. Increasing the frequency of voiding can reduce radiation dose to the normal organ receiving the highest radiation absorbed dose, the bladder wall. Potential radiation risks associated with a typical PET study utilizing this agent are within generally accepted limits.

Although each organ will receive a different dose, the maximum amount of radiation exposure subjects will receive from this study is equal to an effective dose equivalent of 2.9 rem for a total of up to 2 injections of 5mCi [^{18}F]FMISO (10mCi total) plus up to 6 attenuation correction CT scans (3 CTs per PET scan).

Previous Human [F-18]FMISO Imaging Studies: Positron emission scanning with [^{18}F]FMISO has been studied for hypoxia in a variety of tumors, including brain cancer, head and neck cancer, lung cancer, sarcoma, rectal cancer, and etc. as well as ischemic stroke over the past 20 years in Australia, Switzerland, Denmark, Germany and in the United States under RDRC approval or its equivalent. Several published studies from the United States are from the University of Washington in Seattle since 1994. Please refer to FMISO IB 2013 for detail)

2.3 Rationale

2.3.1 Hypoxia and Homologous Recombination DNA Repair

Hypoxia is one of the characteristics of the microenvironment in growing tumors. 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. Hypoxia is also induced when highly proliferative tumor cells distance themselves from an oxygen supply.[43] The changes that a tumor cell must undergo to survive the metabolic challenges imposed by a low oxygen state are multiple. 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.[43-45]

Dr. Peter Glazer' group at Yale University and others have shown that hypoxia also induces genomic instability and gene silencing, especially of the genes that are involved in DNA repair mechanisms. Among others, his lab has shown that hypoxia can induce homologous recombination DNA repair defects by transcriptional repression *of RAD51, BRCA1* and *BRCA2* in numerous human cell lines derived from a wide range of tissues using quantitative PCR and Northern blotting, including MCF7 (breast), A549 (lung adenocarcinoma), RKO (colon), CaCo-2 (colon), PC3 (prostate) and DU145 (prostate) [46]. Subsequent work reported that, as expected, PARP inhibitors displayed increased cytotoxicity against A549 (lung adenocarcinoma), RKO (colon) and H460 (lung adenocarcinoma under hypoxic conditions, compared to normoxic conditions[47]. Interestingly, they also reported that disruption of PARP function, either via chemical PARP inhibitors or siRNAs targeted to PARP-1, can inhibit HDR by suppressing expression of BRCA1 and RAD51 regardless of oxygenation status, and the addition of hypoxic conditions to PARP inhibition enhanced the down regulatory effect. In addition, transcription of RAD51 and MLH1 also decreased in response to hypoxia via a similar mechanism [46, 48-51]. Posttranslational modifications of histones have been described as an important epigenetic mechanism of gene regulation [52-54]. 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 [55]. 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 [55], that is thought to trigger angiogenesis.

The acquired homologous recombination defect (HRD) with downregulation of BRCA1/2 is an important observation and may have therapeutic implications for the use of PARP inhibitors.

2.3.2 Cediranib as an inducer of hypoxia

Cediranib is a potent VEGFR tyrosine kinase inhibitor (VEGFR TKI) with activity against VEGFR-1, -2, -3 and c-Kit [22, 23, 25]. Cediranib has been shown to inhibit endothelial cell proliferation, survival and angiogenesis, and has shown activity against a broad range of tumor xenografts [22, 56, 57]. Cediranib as an inhibitor of VEGF signaling through its

action on VEGFRs, has been shown in preclinical models to inhibit vascular permeability and perfusion measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) [58-60]. In the First-Trial-In-Man (FTIM) study in patients with advanced solid tumors, pharmacodynamic assessment demonstrated time-, dose- and exposure-related decreases in initial area under the curve, defined over 60 seconds post-contrast arrival in the tissue (iAUC60) using DCE-MRI [61]. These data were confirmed in additional clinical studies [62, 63]. In subcutaneous xenografts combined carbogen USPIO MRI also revealed decreases in perfusion following cediranib treatment [64]. Hypoxia was measured in parallel by using pimonidazole and histologic assessment after sacrificing the animals. A significant 40% increase in tumor hypoxia was observed. 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 [65].

2.3.3 Clinical Studies of the combination of cediranib and olaparib

In a randomized open-label phase 2 study, patients with platinum-sensitive, relapsed, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer, or those with deleterious germline *BRCA1/2* mutations, were randomized to receive olaparib capsules 200 mg twice daily or the combination of cediranib 30 mg daily and olaparib capsules 400 mg twice daily **[66]**. The primary endpoint was PFS analyzed in the intent-to-treat population. Median PFS was 17.7 months (95% CI 14.7–not reached) for the women treated with cediranib plus olaparib compared with 9.0 months (95% CI 5.7–16.5) for those treated with olaparib monotherapy (hazard ratio 0.42, 95% CI 0.23–0.76; p=0.005). In a post-hoc, subgroup analysis by germline BRCA mutation (gBRCAmt) status, the magnitude of the difference between the two arms was even more striking in those with wild-type *BRCA* or unknown status (wtBRCA/unk) than in those with gBRCAmt. Among the wtBRCA/unk, the hazard ratio (HR) of PFS for the combination versus olaparib monotherapy was 0.32 (95% CI 0.14–0.74, p=0.008) whereas among mtBRCA, the HR was 0.55 (95% CI 0.24-1.27, p=0.16). The difference in median PFS was 8.7 months (9 vs 17.7 months in olaparib vs cediranib plus olaparib, respectively) in the wtBRCA/unk, whereas the difference in median PFS was only 2.9 months (16.5 vs 19.4 months) in the mtBRCA. While data from a post-hoc analysis data must be interpreted with caution, nonetheless, this is hypothesis-generating and supports further investigation to elucidate the mechanism of the potential synergy especially in those with BRCA wild-type.

2.3.4 **Summary of Rationale**

Cediranib, by inhibition of VEGF-signaling decreases vascular permeability and perfusion and induces hypoxia in tumors. Hypoxia as a consequence may downregulate BRCA1 expression through multiple mechanisms, as well as at the same time upregulate VEGF expression. Downregulation of BRCA1 may lead to a BRCA loss phenotype and tumors via this mechanism may become more sensitive to olaparib, a PARP inhibitor. The hypothesis that cediranib may render tumors more sensitive to olaparib will be tested in this study and multiple correlative endpoints elucidate underlying mechanisms.

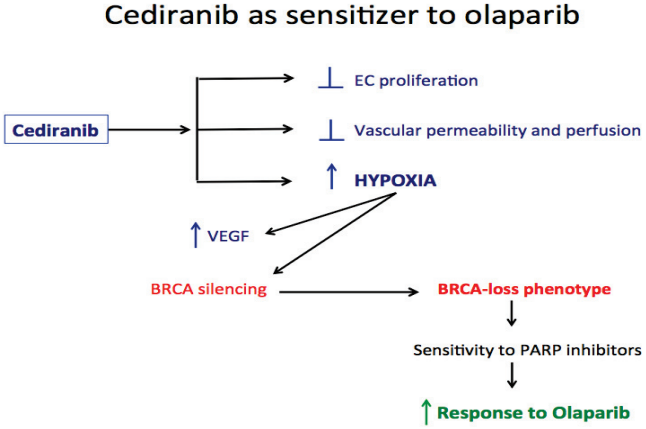


Figure 2: Summary of Rationale

2.4 Correlative Studies Background

2.4.1 Introduction

The hypothesis that cediranib may render tumors sensitive to olaparib treatment via induction of hypoxia and downregulation of BRCA1, will be tested in this study. While evidence from multiple preclinical and clinical studies exists for each step of the hypothesis, this has not been tested in a single clinical study. However data exist showing increased efficacy of the combination over olaparib monotherapy in patients without germline BRCA mutation [66].

The correlative studies described below will focus on generating data to test the hypothesis. It is proposed to explore the induction of hypoxia in patient's tumors after single agent cediranib treatment using FMISO PET imaging in the NSCLC cohort. From all patients, blood samples at multiple time points will be obtained to measure VEGF (and other vascular and angiogenic markers) as well as circulating tumor DNA (ctDNA). The markers will be correlated with each other and outcome. Tissue and blood markers will be exploratory.

In addition, the use of the BROCA panel is planned as in integrated marker in the study for all study patients. In addition to testing the tumors, a blood sample will be obtained at baseline for germline BROCA testing.

It is likely that the variants / mutations in the genes included in this panel will influence the response to olaparib therapy. The panel is currently studied in ovarian studies using the combination of cediranib and olaparib and this study will be the first to study the BROCA panel outside of ovarian cancer.

2.4.2 **[^{18}F]FMISO imaging for tumor hypoxia (Drs. Ming-Kai Chen, Richard Carson, David Carlson, Yale University)**

Fluorine-18 labeled misonidazole, 1H-1-(3-[18F]-fluoro-2-hydroxy-propyl)-2-nitro-imidazole, or [18F]FMISO, is a radiolabeled imaging agent that has been used for investigating tumor hypoxia with positron emission tomography (PET). An ideal hypoxia-imaging agent should distribute independently of blood flow, which is best achieved when the partition coefficient of the tracer is close to unity. Under these circumstances, imaging can be done at a time when the intracellular tracer distribution has equilibrated with the tracer in plasma near the cells. [18F]FMISO is an azomycin-based hypoxic cell sensitizer that has a nearly ideal partition coefficient and, when reduced by hypoxia, binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration, rather than by any downstream biochemical interactions. [67]

Since its development [68], numerous studies, both pre-clinical and clinical, consider [^{18}F]-FMISO and PET imaging to be the most promising method for hypoxia quantification, since the tracer binds in hypoxic cells selectively [69-72]. As a result, it is a lead contender in the *in vivo* and clinical assessment of hypoxia and is the most extensively studied PET hypoxia tracer [73, 74]. Koh *et al.* [69] and Valk *et al*. [70] first demonstrated that [^{18}F]-FMISO could detect hypoxia in human tumors. Rasey *et al*. [71] further validated the tracer sensitivity as a hypoxic marker in 37 patients and confirmed the prevalence, presence, and variability of hypoxia in human tumors. Bruehlmeier *et al*. [75] also supported the use of [^{18}F]FMISO for hypoxia quantification and showed the lack of influence of perfusion and the blood-brain-barrier on tracer hypoxia detection. This implies tracer differentiation and specificity. Only Bentzen *et al*. [76] has shown an inability for [^{18}F]FMISO to detect hypoxia in human tumors. However, this discrepancy could be attributed to the trial protocol design, as [^{18}F]-FMISO was used to characterize tumors, not to explicitly detect hypoxia. Most significantly, Gagel *et al*. [77] showed the tracer was representative of intracellular pO_2 as [^{18}F]-FMISO uptake correlated with Eppendorf pO_2 probe measurements, while this was not the case for [^{18}F]-FDG, a tracer for glucose metabolism [78]. Statistically significant correlations have also been found between [^{18}F]FMISO uptake and immunohistochemistry staining [79-81] for HIF1-alpha hypoxic-inducible factor [76]. Okamoto *et al*. [82] showed that [^{18}F]FMISO PET could provide reproducible hypoxic volumes in H&N cancer patients. In the clinic, [^{18}F]FMISO has been shown to detect hypoxia in a variety of tumor types from soft-tissue sarcoma, H&N cancer, non-small cell lung cancer, breast cancer, and brain tumors [71, 77, 83-86].

In this study, the PET/CT imaging of hypoxia with [^{18}F]FMISO will be performed at baseline and following cediranib monotherapy in the NSCLC cohort. Please see Section 5.1.3 for detail.

2.4.3 Angiome Panel (Dr. Andrew Nixon, Duke)

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 [87]. 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 [88] and CALGB90206 was a phase III study of IFN +/- bevacizumab in 1st line mRCC [89]. Both of these studies found that high levels of IL6 predicted for greater benefit from these VEGF inhibitors [90, 91]. The CALGB study with bevacizumab also found a predictive role for HGF that was IL-6 dependent (i.e., a 3-way treatment interaction) [90]. 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 [92, 93]. Tumor angiogenesis, inflammation, and anti-tumor immunity have highly interconnected biologies, a topic that has been extensively reviewed [94-96]. 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

2.4.4 Circulating Tumor DNA - Plasma (Dr. Abhijit Patel, Yale)

For many types of cancer, serum protein biomarkers to monitor therapeutic efficacy either do not exist or are not very robust. For example, there are currently no blood biomarkers that are in routine clinical use to track response to therapy in patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). In patients with advanced breast and pancreatic cancers, the blood markers CA 27.29, CEA, and CA 19-9 can be used to monitor treatment response and to detect disease progression. However, these markers suffer from lack of cancer specificity, as serum levels can be elevated in patients with other types of cancer and can also be elevated in non-malignant conditions such as cirrhosis, inflammatory bowel disease, hepatitis, and renal impairment, among others. Moreover, serum levels of protein markers typically change gradually, making it difficult to obtain a rapid assessment of the effectiveness of a therapy. Thus, new blood biomarkers with greater specificity and faster response kinetics could provide a more reliable and rapid assessment of treatment efficacy to guide therapeutic decision-making.

Recent technological advances have made it possible to detect and quantify small amounts of cell-free tumor-derived DNA fragments in the bloodstream of patients with various types of cancer [97-102]. Such circulating tumor DNA (ctDNA) is believed to be released from dying cancer cells, and is showing excellent promise as a cancer biomarker [103, 104]. Tumor-derived DNA can be distinguished from normal background cell-free DNA in plasma based on the presence of tumor-specific somatic mutations. Because somatic mutations are a hallmark of cancer, circulating tumor DNA should in principle be identifiable in all types of malignancies. False-positive results are expected to be extremely uncommon since cancer-associated mutations should rarely be found in plasma in the absence of malignancy. Furthermore, because there is no physiologic background level, a small amount of mutant DNA released from a small tumor should be detectable if the technical background (error rate) of the assay can be minimized. It has also been observed (in our lab and by others) that ctDNA exhibits much more rapid posttreatment kinetics than protein markers. Most protein markers typically show a decline with successful therapy over several months, whereas ctDNA can show a dramatic decline within **~2-3 weeks** [102]. While most protein markers are secreted by living and growing cancer cells, ctDNA is a byproduct of dying cancer cells, and it is rapidly cleared from the blood with a half-life of ~2 hours [105]. Thus, ctDNA provides a real-time estimation of active tumor cell death, rather than simply a measure of tumor burden. In several cases, we have observed an initial spike in ctDNA levels within the first few days after beginning treatment (likely due to tumor kill), followed by a substantial decline below pre-treatment levels after the initial wave of cell death has subsided. This can lead to an

exaggerated difference between pre- and post-treatment levels, suggesting that ctDNA may be a more responsive marker of therapeutic efficacy.

Patel laboratory has developed an ultrasensitive assay for measuring small amounts of cell-free mutant DNA released into the blood from dying tumor cells[102, 106]. The assay uses next-generation sequencing combined with novel error suppression techniques to enable measurement of rare mutant ctDNA down to a fractional abundance of ~0.02%. Coverage of a broad panel of mutation-prone genomic regions ensures that ctDNA can be detected in the majority of patients with common solid malignancies. The assay has been tested on over 1500 clinical samples thus far. Indeed, in patients receiving chemotherapy, targeted therapy, surgery, or radiation therapy, we have observed that ctDNA levels usually decrease substantially during successful treatment (sometimes with a transient spike due to tumor kill). However, longitudinal testing of the assay has been performed mostly on heterogeneous populations of patients who were treated with a variety of regimens. To more rigorously evaluate the performance of the assay, here we plan to obtain blood samples at well-defined intervals from a population of patients having 4 different types of cancer, all receiving uniform treatment in the setting of a clinical trial.

2.4.5 BROCA Panel (Dr Elizabeth Swisher, University of Washington, Seattle)

The BROCA-HR assay will be used in the study to assess correlation of response and effect of homologous recombination deficiency (HRD) status, on the effectiveness of targeted therapy with cediranib in combination with olaparib. BROCA testing will be performed on the tumor samples as well as a germline blood sample obtained at baseline.

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 [107-111]. 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 [112]. PARP inhibitors (PARPi) demonstrate synthetic lethality in cells with HRD, including cells deficient in *BRCA1/2* [34, 113]. 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 [114]. Importantly, approximately 25% of serous ovarian cancers that are wildtype for *BRCA1/2* also respond to PARPi [40].

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 [112, 115] and also appear to confer sensitivity to PARPi [116]. PARPi also selectively kill cells *in vitro* that are deficient in other (HR) genes including *RAD51D, NBN, ATM,* and *CHEK2* [107, 117]. 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 [115].

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 [118, 119]. 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 [120-122]. 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 [37]. 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 [123, 124]. 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 [125]. 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) [125, 126].* 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) [127]. 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 (Pennington, Swisher et al. manuscript in progress). Germline and somatic loss of function mutations were identified in all of the 13 FA/HR genes evaluated.

Dr. Swisher's laboratory has 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* [128-130]. 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.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed, metastatic or unresectable malignancy of the following types: (a) non-small cell lung cancer (NSCLC), (b) triple-negative breast cancer (TNBC; defined by ER<1%, PR<1% and HER2 1+ or less by IHC; if HER-2 expression is 2+, a negative FISH testing is required) (c) pancreatic adenocarcinoma (PDAC), or (d) small cell lung cancer (SCLC).

3.1.2 Must have received at least one line of standard systemic treatment for locally advanced or metastatic disease setting of the respective tumor type. For NSCLC, it is either PD-1/PD-L1 inhibitor, or platinum-containing chemotherapy, or an EGFR tyrosine kinase inhibitor or an ALK inhibitor if sensitizing mutation present; TNBC: platinum-containing chemotherapy; PDAC: 5-FU-, gemcitabine-, or taxane-containing chemotherapy either with or without radiation therapy; SCLC: platinum-containing chemotherapy for limited or extensive stage disease.

3.1.3 Patients must have measurable disease by RECIST v1.1. See Section 11 for the evaluation of measurable disease.

3.1.4 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 prior grade 2 treatment-related hypothyroidism requiring treatment, provided Free T4 within normal range, may be considered eligible after discussion with the study Principal Investigator (PI).

3.1.5 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.

3.1.6 ECOG performance status 0, 1 or 2 (Karnofsky ≥50%, see Appendix A).

3.1.7 Life expectancy of ≥4 months.

3.1.8 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– hemoglobin	>9 g/dL
– total bilirubin	≤1.5 × the institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN
– creatinine	≤1.5x ULN OR
– creatinine clearance	≥45 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal. The creatinine clearance is calculated using Cockcroft-Gault formula as follows: Cockcroft-Gault CrCl = (140-Age)* (Wt in Kg) * (0.85 if female) / (72*Cr)
– Proteinuria	a urine protein:creatinine ratio of <1, or <1 g protein on 24-hour urine collection

– Coagulation parameters (INR, aPTT)	within 1.25 × ULN institutional limits, except where a Lupus anti-coagulant has been confirmed

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

3.1.10 Adequately controlled thyroid function defined by Free T4 within normal range, with no symptoms of thyroid dysfunction.

3.1.11 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.

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

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

3.1.13 The effects of cediranib and olaparib on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 4 months after completion of cediranib and olaparib administration.

3.1.14 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 or RT within 3 weeks prior to start of the study agents, or those who have not recovered from adverse events due to agents administered more than 3 weeks earlier.

3.2.2 Patients should not have received any other investigational agents within the past 4 weeks.

3.2.3 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 should be excluded from this clinical trial, since neurologic dysfunction may confound the evaluation of neurologic and other AEs. Screening Brain MRI (or CT if MRI contraindicated) will be required for patients with recurrent NSCLC, TNBC, or SCLC. Brain MRI (or CT if MRI contraindicated) is required for PDAC ***if*** clinically suspected by patient's symptoms or neurological exam. Should patient found to have brain metastasis, treatment of brain metastasis must precede the participation in this study. For patients with known and treated brain metastases is allowed in this study if they fulfill the following criteria:

- The lesions have improved or remained stable radiographically and clinically for at least 6 weeks after completion of brain irradiation or stereotactic brain radiosurgery and off steroids for at least 6 weeks.

3.2.4 Patients who have received prior inhibitor of VEGF signaling and a PARP inhibitor administered in combination. Unless administered in combination, patients who received a prior PARP inhibitor or a prior VEGF-signaling inhibitor agent are allowed after discussing with the PI.

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

3.2.6 Participants receiving any medications or substances that are *strong* inhibitors or inducers of CYP3A4 (See Appendix C) are ineligible. Dihydropyridine calcium-channel blockers are permitted for management of hypertension.

3.2.7 Current use of natural herbal products or other complementary alternative medications (CAM) or "folk remedies."

3.2.8 Patients with concomitant or prior invasive malignancies within the past 3 years. Subjects with treated limited stage basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the breast or cervix are eligible.

3.2.9 Uncontrolled intercurrent illness including, but not limited to, 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.

3.2.10 History of myocardial infarction within 6 months prior to registration.

3.2.11 History of stroke or transient ischemic attack within 6 months prior to registration.

3.2.12 NYHA classification of III or IV.

3.2.13 Current cardiac arrhythmia requiring concurrent use of anti-arrhythmic drugs

3.2.14 History of hypertensive crisis or hypertensive encephalopathy within 3 years prior to registration.

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

- An US within the last 6 months prior to registration will be required to document that it is ≤ 5cm
- patient must be asymptomatic from the aneurysm
- Blood pressure must be well controlled as defined in this protocol.

3.2.16 A major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to starting cediranib (percutaneous/endobronchial biopsies are allowed).

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

3.2.18 History of hemoptysis or any significant bleeding within the last 1 month prior to enrollment.

3.2.19 Presence of cavitation of central pulmonary lesion

3.2.20 History of abdominal fistula, intra-abdominal abscess, or gastrointestinal perforation within the 3 months prior to enrollment.

3.2.21 Patients may not have current dependency on IV hydration or total parenteral nutrition (TPN).

3.2.22 Patients may not have evidence of coagulopathy or bleeding diathesis. Therapeutic anticoagulation for prior thromboembolic events is permitted. The clinical indication for therapeutic anticoagulation must be clearly documented prior to enrollment and must be discussed with the P.I. Given the increased risk of serious bleeding from cediranib, patients who are on greater than or equal to 2 anti-thrombotic agents, including but not limited to anti-platelet agents (NSAIDs/aspirin, clopidogrel), heparin, LMWH, warfarin, and a direct thrombin inhibitor, will be excluded.

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

3.2.24 Pregnant women are excluded from this study because olaparib and cediranib have the potential for teratogenic or abortifacient effects. Due to the fact that there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with olaparib and cediranib, breastfeeding should be discontinued if the mother is treated with cediranib and olaparib.

3.2.25 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with cediranib or olaparib. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated. HIV-positive patients with undetectable viral loads and CD4 counts >300, and not on any antiretroviral therapy may be allowed after discussing with the principle investigator.

3.2.26 Any condition that, in the opinion of the treating investigator would interfere with evaluation of the investigational product or interpretation of subject safety or study results.

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 a site is interested in participating in this study, it is **highly recommended** that an investigator or his/her team at the participating site reach out to the Study PI via email: joseph.w.kim@yale.edu to discuss their interest in the participation.

Each investigator or group of investigators at a clinical site must obtain IRB approval for

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

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

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

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

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

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 9881 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 *#9881.*
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 9881 Site Registration:

- Send an email to the Study PI: joseph.w.kim@yale.edu to obtain approval to participation in this study.
- 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) (All sites)
- Local informed consent document (All sites)
- CTEP ISCG Approval of International Site Participation Site Participation (International sites only)
- LPO Approval of International Site Participation (International sites only)
- Clinical trial Site information Form (California sites only)
- Qualified Investigator Undertaking (California sites only)
- Research ethics Board Attestation (California sites only)

4.2.3 Submitting Regulatory Documents

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

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

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

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

4.2.4 Checking **Site** Registration Status

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

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

Note: The status given only reflects compliance with IRB documentation and institutional

compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

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

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

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

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

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

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

4.3.3 OPEN/IWRS Questions?

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

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7802 or Theradex main number 609-619-7862; CTMSSupport@theradex.com.

4.4 General Guidelines

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

5. TREATMENT AND/OR IMAGING PLAN

Cycle1 is 35 days long and remaining cycles are 28 days long.

5.1 Agent Administration

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

Dose level	Cediranib Tablet
-2	15 mg daily, orally
-1	20 mg daily, orally
1 (starting dose)	30 mg daily, orally

Dose Level	Olaparib Tablet
-2	100 mg twice daily, orally
-1	150 mg twice daily, orally
1 (starting dose)	200 mg twice daily, orally

NOTE: Dose modification will be done independent of each other.

5.1.1 Cediranib

Cediranib dosing will start at 30mg orally on day 1 of each cycle (See Study Calendar for detail).

Cediranib at the appropriate dose level will be given orally every 24 hours (+/- 2 hours) 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 should be taken on an empty stomach approximately one hour (+/- 30 mins) before the morning dose of olaparib.

Cediranib will be dispensed at the start of each cycle. Patients will be provided with a pill diary for each drug (Appendix E (cycle 1) and Appendix F), instructed in its use, and asked to bring it with them to each appointment.

5.1.2 **Olaparib**

For those undergoing FMISO scans (NSCLC), olaparib 200mg twice a day, orally, is to start on the day after the second FMISO scans after the second set of research blood is collected. See Study Calendar for detail.

For the rest of patients, olaparib 200mg twice a day, orally, is to start on Day 4 of cycle 1 after the second set of research blood is collected. See Study Calendar for detail. In case of scheduling conflicts, olaparib may start on any day between 4 and 7.

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 (+/- 2 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 should be taken approximately 1 hour (+/- 30 mins) after the cediranib dose, with a light meal/snack. 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.

Olaparib will be dispensed at the end of cediranib monotherapy of cycle 1 (to minimize the confusion for the patient during the monotherapy lead-in period), and at the start of the subsequent cycles.

Patients will be provided with a pill diary (Appendix E (cycle 1 diary) and Appendix F), 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.

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.

5.1.3 **[18F]Fluoromisonidazole (FMISO)**

Schedule:

Please refer to the Study Calendar for the schedule of the scans.

[F-18]FMISO Administered Dose:

[F-18]FMISO will be administered to subjects over 1 minute by intravenous bolus injection. Doses will be pre-calibrated to 5 mCi, with a dose range of 4-5 mCi. The dose will not exceed 5 mCi total.

[F-18]FMISO-PET Imaging:

Imaging Acquisition:

Up to imaging-evaluable twenty patients with NSCLC will undergo 2 [^{18}F]-FMISO PET/CT scans of the thorax. The first baseline scan will be obtained after the biopsy, the second scan will be acquired after cediranib monotherapy. Each dynamic [^{18}F]-FMISO PET scan consists of 3 parts and a CT will be performed before each part for attenuation correction. PET scans will be acquired from 0-120mins, 150-180mins, and 210-240 mins post IV automated injection of a 4-5 mCi bolus of [^{18}F]-FMISO. Alternatively, a short protocol of dynamic FMISO PET scans could be acquired from 0-60 min and 90-120 min. PET/CT scans will be performed on the Siemens Biograph mCT PET/CT scanner at Yale PET center or other similar PET scanners at other institutions. An intravenous line will be placed for venous blood sampling at pre-determined times to provide an accurate value of the [^{18}F]-FMISO activity input function.

Imaging Analysis:

Tumor regions will be defined from the CT and PET images. A number of quantification measures will be used to compare pre- and post-drug hypoxia levels, including standardized uptake values (SUV), hypoxic volumes (HV), as well as tracer compartment kinetic modeling measures. Tumor to blood ratio (TBR) is defined as the ratio of the [^{18}F]-FMISO signal in each tumor voxel in the tumor region of interest (ROI) summed from 210-240 min or 90-120 min (from short protocol) to the average signal in heart over the same time frame post-injection. Threshold values used to define HVs by [^{18}F]-FMISO imaging impact the reliability and robustness of hypoxia quantification. Using a defined TBR threshold >1.2, HV percentages (fraction of tumor that is hypoxic) will be calculated based on absolute tumor volume defined by CT [131]. (Cheng J. *J Nucl Med. 2013*)

Image Interpretation:

The summed [^{18}F]-FMISO imaging will be interpreted by experienced nuclear medicine physician visually, using a scoring system according to Rischin et al. (J Clin Oncol. 2006;24:2098–2104). This scoring system has 5 classes: 0=uptake less than background; 1=no regions of focal uptake greater than background; 2 = focal uptake mildly greater than background; 3=focal uptake moderately greater than background; and 4=focal uptake markedly greater than background. In a second step, these 5 classes will be grouped into 2 classes and a score ≥ 2 is considered positive for hypoxia.

TBR and HV imaging (TBR>1.2) will be generated and reviewed as well. HV will be calculated based on absolute tumor volume defined by CT.

The interpretation will be done centrally by Yale investigators. The FMISO imaging must

mailed to Dr. Ming-Kai Chen at the following address **within 1 week** of completing a pair of FMISO PET/CT scans:

Positron Emission Tomography (PET) Center
Yale University
801 Howard Avenue
PO Box 208048
New Haven, CT 06520-8048
Ph: (203) 737-YPET
Fax: (203) 785-3107
Email: ming-kai.chen@yale.edu

The CT of the FMISO will not be used for disease assessment.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of AZD2171 (cediranib) and olaparib (AZD2281) with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. *In vitro* studies demonstrate that olaparib (AZD2281) is primarily metabolized by CYP 3A4/5 enzymes. Potent inhibitors or inducers of CYP 3A4/5 may be prohibited or used with caution. The study team should check a frequently-updated medical reference for a list of drugs to avoid or use with caution. Appendix C provides a list of drugs that are prohibited. Appendix D (Patient Drug Information Handout and Wallet Card) should be provided to patients.

Cediranib demonstrated minimal inhibitory effects on the activity of CYP3A4 (testosterone and midazolam) *in vitro*, although the IC_{50} was far in excess of the clinically relevant concentrations. In vitro studies suggested that CYP enzymes were not significantly involved in the production of the principle human metabolites of cediranib, therefore co-administration of known inhibitors or inducers of hepatic CYP enzymes would not be expected to have significant effects on the clearance of cediranib.

Olaparib did not cause significant inhibition or induction of P450 isozymes. However, *in vitro,* cytochrome P450 (CYP) 3A4 (CYP3A4) and 3A5 (CYP3A5) were shown to be the major isozyme responsible for the metabolism of olaparib. Modelling and simulation suggests olaparib clearance may be increased by co-administration with rifampicin (a CYP3A4 inducer) and decreased by co-administration with itraconazole (a CYP3A4 inhibitor). Given these data, potent inhibitors or inducers of CYP3A4 (See Appendix C) must not be used during this study for patients receiving olaparib. Dihydropyridine calcium-channel blockers are allowed for management of hypertension.

Patient should receive general concomitant and supportive care medications based on best medical practice.

Primary prophylaxis with G-CSF or other bone marrow-supportive agents, including erythropoiesis-stimulating agents, is not allowed. (See Section 6 for Management of Febrile Neutropenia)

The use of any natural/herbal products or other "folk remedies" is not allowed on study. All medications must be recorded in the case report form and be reviewed by the treating physician at each visit.

Frequent blood pressure monitoring is important in patients receiving cediranib. Experience to date suggests that increases in blood pressure may occur following dosing with cediranib for a number of weeks and that these increases may occur over a relatively short time frame. It is imperative that the investigator institute appropriate measures to control BP. This may necessitate changes to existing antihypertensive medication, addition of new medication(s), and/or interruption/withdrawal of cediranib. Patients will be provided blood pressure cuffs and must be able and willing to monitor their blood pressure on a twice daily basis. Section 6 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension.

Diarrhea should be managed with loperamide: 4 mg at first onset, then 2 mg every 2-4 hours until diarrhea is controlled (maximum = 16 mg loperamide per day). Additional guidelines for management of diarrhea are presented in Section 6.

5.3 Duration of Therapy

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

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

When a decision is made to discontinue study treatment, an evaluation listed under End of Treatment **(EOT)** will be performed (See Study Calendar), unless patients withdraws consent to undergo EOT evaluation.

5.4 Duration of Follow Up

- Patients will be followed for 4 weeks after discontinuing study treatment or until death, whichever occurs first, for a clinical assessment of any significant treatment related AE.
- Patients who discontinue the study treatment for reasons other than disease progression or withdrawal of consent, will be followed via a clinic visit, a phone call by a study team, or obtaining medical records, every 4 weeks until disease progression, start of new therapy, or death, whichever occurs first.
- Patients who discontinue the study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event, or until radiographic documentation of disease progression as noted above, start of new therapy, or death, whichever occurs first.
- If patients discontinue study treatment due to withdrawing consent, no further follow-up will be performed.

5.5 Criteria for Removal from Study

Patients will be removed from the study when any of the following happens, whichever occurs first:

- Completion of study Follow Up as outlined in Section 5.4
- Death
- Lost to follow-up
- Withdrawal of consent

6. DOSING DELAYS/DOSE MODIFICATIONS

Hematologic Parameters for Treatment

Patients must meet the following absolute neutrophil count (ANC) and hematologic parameters for treatment. Additionally, dosing parameters for hematologic AEs in Section 6.2 should be observed.

- Cycle 1, Day 1:
  - ANC $\geq$ 1500/mm^3
  - Platelets $\geq$ 100,000/mcL
  - Hemoglobin > 9 mg/dL

- Cycles 2 and beyond, Day 1:
  - ANC $\geq$ 1000/mm^3
  - Platelets $\geq$ 100,000/mcL
  - Hemoglobin $\geq$ 8 mg/dL

All Cycles, Day 1

Patients must meet the following parameters on day 1 of each cycle to proceed with treatment. Patients who do not meet these criteria may resume treatment later in the cycle once criteria are met. Cycles and days are numbered continuously regardless of any dose holds or delays in resumption of treatment.

- Adequate blood pressure control, as detailed in Section 6.3

- Serum creatinine ≤ 1.5 x the institutional upper limit of normal
- Liver function tests (AST and ALT) ≤ 2.5 x the institutional upper limit of normal
- ECOG performance status of 0, 1 , or 2
- No evidence of life-threatening medical problems
- Urine protein:creatinine ratio OR urine dipstick protein as detailed in Section 6.4

6.1 Cediranib and Olaparib Dose Modification Tables

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

Dose level	Cediranib
-2	15 mg daily, orally
-1	20 mg daily, orally
1 (starting dose)	30 mg daily, orally

Dose Level	Olaparib Tablet
-2	100 mg twice daily, orally
-1	150 mg twice daily, orally
1 (starting dose)	200 mg twice daily, orally

Dose modification will be done independent of each other.

6.2 General Management of Adverse Events

The management of general adverse events not otherwise specified will be as per the table below. Management of specific toxicities, including hypertension, proteinuria, decreased in LVEF, diarrhea, fever and neutropenia, nausea and vomiting, thyroid toxicities, reversible posterior leukoencephalopathy syndrome (RPLS), and gastrointestinal perforation will be as further outlined in specific sections 6.3-6.11.

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

General Management of Adverse Events (Non-Hematologic)

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) 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)
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 14 days until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.1, 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 14 days 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 14 days until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.1, at the treating investigator's discretion.[2] The study PI of the study should be informed regarding all dose modifications.
1. Grade 3 or 4 non-hematologic AE related to cediranib and olaparib combination that does not resolve to grade 0-2 within 14 days despite maximum supportive care after treating patient at the lowest reduced dose level.[3] 2. Grade 3 or 4 non-hematologic AE related to cediranib/olaparib lasting >14 days despite maximum supportive care and treatment being held.	Remove patient from study.

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

General Management of Adverse Events (Hematologic)

Observation	Action
Absolute neutrophil count ≥1000/mcL **AND** Platelets ≥100,000/mcL **AND** Hemoglobin ≥8 mg/dL	Maintain dose level.
Absolute neutrophil count <1000/mcL **OR** Platelets <100,000/mcL **OR** Hemoglobin <8 mg/dL	Hold treatment for up to 14 days until absolute neutrophil count ≥1000/mcL, platelets ≥100,000/mcL, and hemoglobin ≥8 mg/dL. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.1, at the treating investigator's discretion. The study PI of the study should be informed regarding all dose modifications. Patients whose counts have not recovered to absolute neutrophil count ≥1000/mcL, platelets ≥100,000/mcL, and hemoglobin ≥8 mg/dL after 14 days should be removed from study.
Grade 4 hematologic AE related to cediranib or olaparib that does not resolve to absolute neutrophil count ≥1000/mcL, platelets ≥100,000/mcL, and hemoglobin ≥8 mg/dL despite maximum supportive care after 14 days.	Remove patient from study.

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

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

6.3 Hypertension (SEE APPENDIX G for Suggested 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 one week, then BP monitoring can be reduced to once daily. Should further hypertension arise, return to twice daily monitoring, until at least one week 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 >2 weeks for management of hypertension, management should be discussed with the study PI and may require discontinuation of protocol therapy.
- 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. 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 reduce the dose of cediranib is expected to cause a decrease in BP. 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) • If patients require a delay of >2 weeks for management of hypertension, discontinue protocol therapy • 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
• Note: Stopping or reducing the dose of cediranib is expected to cause a decrease in BP over several days. Continue to monitor BP twice daily.

The treating physician and patient should monitor BP for hypotension and adjust the number and dose
of antihypertensive medications accordingly.

Event	**Definition**	**Antihypertensive Therapy**	**Blood Pressure Monitoring**	**Cediranib Dose Modification**
Grade 1	Asymptomatic transient (<24 hours) increase by >20 mmHg diastolic or to > 140/90 mmHg if previously WNL	none	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 unless otherwise clinically necessary** *Consider renal consult*	Increase frequency of monitoring until stabilized	Do not hold cediranib unless otherwise clinically necessary
Grade 3	Requiring more than one drug or	Maximize 2 drug regimen	Increase frequency of	Do not hold cediranib unless

	more intensive therapy than previously.	• *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.**	monitoring until stabilized	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	Intensive BP monitoring (hospitalization if necessary)	**Hold cediranib.** If BP is reduced to less than 140/90 within 7 days, cediranib may be resumed at a reduced dose after discussion

		to maximize the full effect of antihypertensive agents.		with the Study PI and/or sponsor.

6.4 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 7 days and repeat UPC and Creatinine assessment. If UPC resolves to <3.5 and Creatinine to ≤1.5x ULN, resume cediranib with reduction in cediranib by one dose level. Consider consultation with nephrologist.
†If UPC is <1.0 and creatinine >1.5x ULN, AE management should be followed as per Table 6.2.		

6.5 Decrease in LVEF

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

1. Prior treatment with anthracyclines
2. Prior treatment with trastuzumab
3. A NYHA classification of II controlled with treatment (see Appendix B)
4. Prior central thoracic RT, including RT to the heart
5. History of myocardial infarction within the prior 12 months

The decision to continue or hold cediranib/olaparib is based on the LVEF as it relates to the institution's lower limit of normal (LLN) **and** change in ejection fraction from screening (LVEF as measured at registration) according to the following table. If the institution's LLN is not specified, an LVEF of 55% should be considered the LLN threshold:

Management and Monitoring of Decreased LVEF

Relationship of LVEF to Institution's LLN	**LVEF Decrease from screening <10%**	**LVEF Decrease from screening 10-15%**	**LVEF Decrease from screening ≥16%**
Normal	Continue	Continue	Continue and repeat[1] MUGA/ECHO within 1-2 cycles
1-5% below LLN	Continue and repeat[1] MUGA/ECHO within 1-2 cycles	Continue and repeat[1] MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles
≥6% below LLN	Continue and repeat[1] MUGA/ECHO within 1-2 cycles	HOLD and repeat[1] MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles
[1]: Repeating ECHO will be at the discretion of the treating physician			

6.6 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.
	If diarrhea persists despite 24 hours of loperamide treatment, hold cediranib for a maximum of 7 days, continue loperamide, and maintain hydration. Cediranib may be restarted at the same dose once patients have been free from diarrhea for 12 hours.
For either persistent grade 2 diarrhea or grade 3 or 4 diarrhea:	Follow General Management of Adverse Events (Non-Hematologic) guidelines in Section 6.2.

6.7 Fever and Neutropenia

Patients who develop fever and neutropenia will be managed via standard medical practice and American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines.

For uncomplicated infections (e.g., community acquired-pneumonia, UTI, cellulitis etc) on oral antibiotic as an outpatient, patient may resume study therapy upon recovery of ANC to ≥1500 and afebrile for at least 48 hrs, while continuing antibiotics

For complicated infections (sepsis, bacteremia), patients will need to recover from fever and active infectious issues prior to **resuming** therapy.

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 of the last dose of study treatment. Study treatment can be restarted at the same dose if an AE of neutropenia or leucopenia have been recovered up to CTCAE Grade ≥1 (ANC ≥1.5 x 109/L). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF). Any subsequent interruptions will require study treatment dose reductions.

6.8 Nausea and Vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. They are generally mild to moderate (CTCAE Grade 1 or 2) severity, intermittent and manageable on continued treatment. No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines.

If a continued anti-emetic is regimen is required, a dose reduction may be considered.

6.9 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.

6.10 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.

6.11 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.

6.12 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.

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)***
	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			

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%)**	
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Generalized muscle weakness		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
	Lethargy		
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 4)***
	Vascular disorders - Other (hemorrhage)[5]		

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

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

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

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

[5]Hemorrhage is a known consequence of VEGF/VEGFR signaling inhibition. The majority of hemorrhage events

reported were mild; however, serious events, defined as symptomatic bleeding in a critical area or organ system (e.g., eye, gastrointestinal tract, genitourinary [GU] tract, respiratory tract, and nervous system) have been reported.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (polycythemia); Bone marrow hypocellular; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (premature ventricular complexes); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Mobitz (type) II atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ears feel full/plugged); Ear and labyrinth disorders - Other (viral labyrinthitis); Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (blindness); Eye disorders - Other (visual disturbance); Papilledema; Photophobia; Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Bloating; Colitis; Colonic obstruction; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Flatulence; Gastric necrosis; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (hydrops); Gastrointestinal disorders - Other (tongue sensitivity); Ileus; Oral pain; Periodontal disease; Peritoneal necrosis; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Fever; Gait disturbance; Hypothermia; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder obstruction; Hepatic pain; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice cholestatic)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture; Injury, poisoning and procedural complications - Other (tracheostomy malfunction); Intestinal stoma leak; Venous injury; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Hemoglobin increased; INR increased; Investigations - Other (elevated ammonia level); Investigations - Other (increased blood erythropoietin); Lipase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Avascular necrosis; Back pain; Bone pain; Chest wall pain; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Myalgia; Myositis; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Central nervous system necrosis; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Encephalopathy; Hydrocephalus; Ischemia cerebrovascular; Memory impairment; Muscle weakness left-sided; Nervous system disorders - Other (coma); Nervous system disorders - Other (right hemiparesis); Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Spinal cord compression; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Confusion; Delirium; Depression; Hallucinations; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Cystitis noninfective; Hematuria; Urinary retention; Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Menorrhagia; Vaginal fistula

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fistula; Pulmonary hypertension; Sinus pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pruritus; Purpura; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (petechiae); Skin and subcutaneous tissue disorders - Other (plantar warts); Skin ulceration; Urticaria
VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hypotension; Vasculitis

Note: Cediranib (AZD2171) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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)***

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%)**	
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
	Urinary tract infection		
INVESTIGATIONS			
	Creatinine increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
		Platelet count decreased	
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)	

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%)**	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	

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

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

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

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

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

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

7.1.1.3 CAEPR for [^{18}F]Fluoromisonidazole (FMISO, NSC 742,836)

Comprehensive Adverse Events and Potential Risks List (CAEPR) for Fluorine-18 Fluoromisonidazole (18F-FMISO, NSC 742836)

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, 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 via AdEERS (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. Below is the CAEPR for Fluorine-18 Fluoromisonidazole (18F-FMISO).

> **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 1.1, July 11, 2018[1]

Adverse Events[2] with Possible Relationship to Fluorine-18 Fluoromisonidazole (CTCAE v5.0 Term)		Specific Protocol Exceptions to Expedited Reporting (SPEER)
	No AEs reported in human studies.	

[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.

Note: No adverse events have been attributed to Positron-Emission Tomography (PET) imaging/diagnostic administration of Fluorine-18 Fluoromisonidazole (18F-FMISO) at the levels described in the Investigators Brochure. Therefore, no adverse events are expected as a result of the intravenous (IV) administration of Fluorine-18 Fluoromisonidazole (18F-FMISO) for typical PET imaging applications such as tumor hypoxia.

Note: As with many IV administered agents, Fluorine-18 Fluoromisonidazole (18F-FMISO) could cause an allergic reaction that could potentially pose a threat to life (anaphylaxis). This has not been observed in limited human exposure to date. Reasonable precautions should be taken, consistent with normal radiologic and clinical facility practice. The patient should be monitored until the PET procedure is completed, and trained personnel and emergency equipment should be available per facility standards.

For purposes of informed consent regarding reasonably foreseeable risks to subjects in trials utilizing Fluorine-18 Fluoromisonidazole (18F-FMISO), the following potential adverse events are considered extremely rare:

- **Injection-related risks that may include infection, or accidental extravasation of the dose that may lead to discomfort, localized pain, or infection.**
- **Risks related to allergic reaction/anaphylaxis that may be life threatening.**

Note: As with all PET imaging agents, Fluorine-18 Fluoromisonidazole (18F-FMISO) is a radiopharmaceutical that decays with positron emission. As such, it poses an intrinsic radiation exposure risk. However, when administered in accordance with the Investigator's Brochure as a PET imaging agent, this risk is felt to be extremely small. The organ and total body doses associated with Fluorine-18 Fluoromisonidazole (18F-FMISO) PET imaging are comparable to or lower than those associated with other widely used clinical nuclear medicine procedures.

Note: Fluorine-18 Fluoromisonidazole (18F-FMISO) 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 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.

The Coordinating Center of the Corresponding Organization is responsible for submitting to the CTSU documentation of AEs that they deem reportable for posting on the CTSU protocol web page and inclusion on the CTSU bi-monthly broadcast.

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 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 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 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 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

[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.

Indicate form for reporting in Rave, timeframes, and if loading of the pathology report is required.

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 AND IMAGING AGENT INFORMATION

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

8.1 CTEP and CIP IND Agents

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. The bottles are child-resistant.

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 20°C to 25°C (68 to 77°F).

Stability: Stability studies are ongoing. Dispense AZD2171 (cediranib) tablets in their original containers. Alternatively, if exact quantity is dispensed in a pharmacy bottle, the supply should be assigned a 30-day expiration.

If a storage temperature excursion is identified, promptly return AZD2171 (cediranib) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

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 green,

film-coated tablets in 100 mg and 150 mg strengths.

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

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

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

Storage: Store in a secure location below 30° C (86° F). 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. In this study, the morning dose should be taken approximately 1 hour after the cediranib dose, with a light meal/snack. The evening dose can be taken with a light meal/snack.

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 [^{18}F]FMISO (Yale DMF)

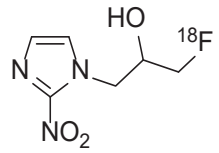
The FMISO will be under NCI's IND but using the Yale DMF.

Chemical name

CAS: 1*H*-Imidazole-1-ethanol, α-(fluoro-^{18}*F*-methyl)-2-nitro-

IUPAC: 1-([^{18}F]Fluoro)-3-(2-nitro-imidazol-1-yl)propan-2-ol

Chemical structure, chemical formula, and molecular weight



Formula: $C_6H_8FN_3O_3$
Molecular Weight: 189.14

CAS registry number

[F-18]: 104613-87-8
[F-19]: 13551-89-8

Synonyms

[F-18]FMISO
Fluoromisonidazole
1-(2-Hydroxy-3-fluoropropyl)-2-nitroimidazole
1-(2-Nitro-1-imidazolyl)-3-fluoro-2-propanol

Abbreviation/Code name

FMISO

Formulary composition

The final product is formulated in about 0.1 mL of absolute ethanol, 10.9 mL of sterile saline, with a final ethanol concentration of ≤1%. Table X is a summary of the components contained in each batch of the formulated drug product.

Final dosage form

Sterile, apyrogenic solution.
Table X. Typical Qualitative and Quantitative Components and Composition for Each Batch of [F-18]FMISO for Injection.

Component	Total Quantity	Unit Quantity
Volume	11 mL	N/A
[F-18]FMISO	≥ 5 mCi	≥ 0.45 mCi/mL
0.9% NaCl Injection, USP	10.9 mL	0.99 mL/mL
Ethanol, absolute, USP	0.1 mL	0.01 mL/mL

Route of administration

Intravenous injection.

Fluorine-18 labeled misonidazole, 1H-1-(3-[^{18}F]-fluoro-2-hydroxy-propyl)-2-nitro-imidazole, or [^{18}F]FMISO, is a radiolabeled imaging agent that has been used for investigating tumor hypoxia with positron emission tomography (PET).

Radiation Dose to Human Subjects
Dosimetry and absorbed dose calculations:

^{18}F is a positron emitter with a half-life of 110 minutes. Intravenously injected [^{18}F]-FMISO distributes throughout the total body water space, crossing cell membranes, including the blood-brain-barrier, by passive diffusion. [^{18}F]FMISO is bound and retained within viable hypoxic cells in an inverse relationship to the O_2 concentration. The uptake of [^{18}F]FMISO in normal human tissues has been measured and used to estimate the radiation absorbed dose associated with the imaging procedure. Dosimetry studies were performed at the University of Washington and have been published in the peer-reviewed Journal of Nuclear Medicine [136]. Briefly, absorbed dose calculations were based on the biodistribution data for [F-18]FMISO in 60 patients (55 males, and 5 females), and were calculated from S values obtained from MIRDOSE 2 according to MIRD. The radiation dose estimates indicate that the maximum permissible single study dosage of [F-18]FMISO, to remain below the 21 CFR 361.1 dose limit, is **64.4** mCi to a 70 kg human subject, (i.e., calculations based upon the urinary bladder wall as the critical organ; 5 rem per single study limit and 0.0777 rem/mCi of [F-18]FMISO to the urinary bladder wall with 2-h voiding intervals.

Tissue	Mean (mGy/MBq)	Mean (mrad/mCi)	Total / 7 mCi (mrad)
adrenals	0.0166	61.4	430
brain	0.0086	31.8	223
breasts	0.0123	45.5	319
gall bladder wall	0.0148	54.8	383
lower large intestine	0.0143	52.9	370
small intestine	0.0132	48.8	342
stomach	0.0126	46.6	326
upper large intestine	0.0140	51.8	363
heart wall	0.0185	68.5	479
kidneys	0.0157	58.1	407
liver	0.0183	67.7	474
lungs	0.0099	36.6	256
muscle	0.0142	52.5	368
ovaries	0.0176	65.1	456
pancreas	0.0179	66.2	464
red marrow	0.0109	40.3	282
bone surface	0.0077	28.5	199
skin	0.0048	17.8	124
spleen	0.0163	60.3	422
testes	0.0146	54.0	378
thymus	0.0155	57.4	401
thyroid	0.0151	55.9	391
urinary bladder wall	0.0210	77.7	544
uterus	0.0183	67.7	474
eye lens	0.0154	57.0	399
Total body	0.0126	46.6	325

Table: Radiation Absorbed Dose to Organs

Availability:
[F-18]FMISO is an investigational imaging agent and will be manufactured at the Yale PET Center under the NCI IND and conforms to the specifications of the NCI IND. [F-18]FMISO has been produced regularly at The Yale PET Center for research use under RDRC.

Single study dose limit

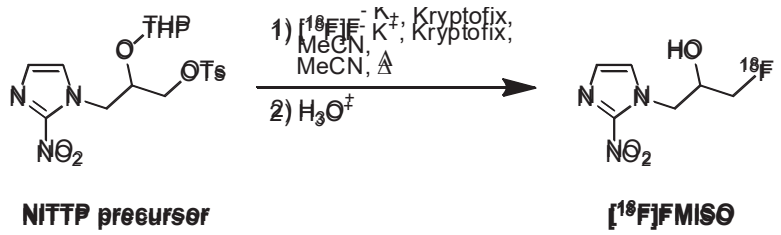
The proposed radioactivity dose is **5 mCi** per single study, which is below the permissible single study of **64 mCi** based on dosimetry calculations.

Method of radioassay

Each dosage of [F-18]FMISO for injection will be assayed in the dose syringe using the F-18 setting of a calibrated Capintec dose calibrator in the dispensing room prior to human subject administration.

Mass Dosage of Active Ingredient
The amount of injected drug is ≤ 15 μg (≤ 79.3 nmol) of FMISO. The use of FMISO at this mass dose is not expected to cause any clinically detectable pharmacological effects nor affect its accumulation in tumor cells in humans. [^{18}F]FMISO has been used in healthy human subjects and patients with different cancers for many years all over the world. There is no evidence that nonradioactive and radioactive FMISO molecules display different biochemical behavior.

Manufacturing of the Radioactive Drug Product
Synthesis of the radioactive drug product is depicted in Scheme 1. Briefly, [F-18]FMISO is synthesized from its *O*-THP- protected tosylate precursor (NITTP) via a bimolecular nucleophilic substitution reaction (S_N2) with [F-18]fluoride in the presence of Kryptofix® 222 followed by cleavage of the protecting group under acidic conditions. Purification with semi-preparative HPLC and formulation of the product with saline followed by terminal sterilization through filtration affords [F-18]FMISO *for injection*. Detailed manufacturing process and specifications for materials and reagents used in the manufacturing processes are described in the Master Batch Record.



Scheme 1. Radiosynthesis of [F-18]FMISO

Quality Specifications of the Radioactive Drug Product

The radioactive drug product *[F-18]FMISO for Injection* will meet the following minimum quality specifications.

Visual appearance

The final *[F-18]FMISO for Injection* shall be clear and colorless with no visual evidence of cloudiness or particulate matter. In addition, there shall be no evidence of breach of integrity of the glass container and respective septum seal.

pH
The pH of the final *[F-18]FMISO for Injection* shall be between 4.6 and 8.

Radiochemical purity
The radiochemical purity shall be ≥ 95% of the sum of all radioactive peaks.

Chemical purity
The maximum mass dose of FMISO shall be ≤ 15 µg per injection, and ≤ 35 µg of other UV absorbing impurities eluting >3 min at 327, 280 or 254 nm (specific impurity at ~4 min ≤3µg/ml; Specific impurity at ~6 min ≤4µg/ml). To maintain this chemical purity specification, the final dose of *[F-18]FMISO for Injection* administered to a human subject, defined by the maximum carrier mass dose of 15 µg and specific activity at the time of injection, will be further adjusted in order to contain no more than 35 µg of non-carrier mass in its impurity content, or 5 mCi, whichever is less, in the final dose administered to a human subject.

Radiochemical identity
The HPLC retention time of [F-18]FMISO shall correspond, within ± 10% variation, to that of the retention time of FMISO, chromatographed under identical conditions.

Specific activity
The specific activity of [F-18]FMISO shall be measured and used to determine the maximum radioactivity dose to be administered that would result in no more than 15 µg of FMISO in a single injection.

Radionuclide identity
Repeat assay of the final *[F-18]FMISO for Injection*, performed using a Capintec dose calibrator of established accuracy, shall result in a calculated $T_{1/2\ physical}$ between 100 and 120 minutes ($T_{1/2\ physical}$ of F-18 = 109.8 minutes).

Bacterial endotoxin level
The final *[F-18]FMISO for Injection* shall contain no more than 175 EU/V of endotoxin level at the expiration time (EU is USP Endotoxin Unit and V is the maximum volume of injection, in mL).

Residual Kryptofix K222 level
The final [F-18]FMISO for injection shall contain no more than 0.05 mg/mL of Kryptofix K222, according to the FDA limit.

Volatile organic impurities
The final *[F-18]FMISO for Injection* shall contain no more than 0.41 mg/mL (i.e., no more than 0.041%, or 410 ppm) of acetonitrile. Acetonitrile is used in the synthesis process and is removed during the evaporation and the semi-preparative HPLC purification procedure. The validation studies and the QC analysis will confirm that the levels of acetonitrile is below the limits in the final *[F-18]FMISO for Injection*.

Sterility
The final *[F-18]FMISO for Injection* shall be sterile. Due to the time constraint imposed by its 109.8 minute radionuclidic half-life, *[F-18]FMISO for Injection* will be dispensed for administration prior to the completion of sterility testing; the latter being initiated as soon as possible after tracer preparation.Note that a final step in the preparation of *[F-18]FMISO for Injection* involves its passage through a sterile, 0.22 μm membrane filter for terminal sterilization, into a commercially available sterile, apyrogenic collection vial.

Routine Quality Control Tests of the Radioactive Drug Product

All QC procedures will be performed on the same portion of sample taken from the final formulation of *[F-18]FMISO for Injection*.

Expiration Dating/Product Stability

The expiration period applied to the *[F-18]FMISO for Injection* will be dependent on the requirement to maintain a radiochemical purity of ≥ 95%. Based on radiochemical stability testing, a maximum expiration period of eight (8) hour post the final formulation of *[F-18]FMISO for Injection* will be applied to the product.

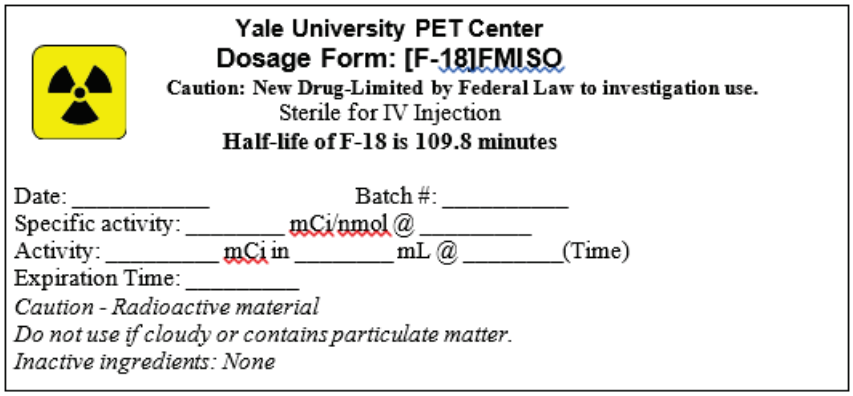
Reprocessing of the Final Product

In accordance with GMP Guidelines § 212.71(d), the final PET drug product may be reprocessed according to written procedures if a batch is rejected for failure to conform or

meet established specifications. For example, reprocessing includes pH adjustment; a second passage through a membrane filter in the event that the membrane failed the integrity test; and re-purification by solid-phase extraction or by HPLC to remove impurities.

Labeling of the Radioactive Drug

The final product vial will be stored in a lead shield. The lead shield will be labeled to include the identity of the product ("*[F-18]FMISO Injection*") and the statements, "Caution: New Drug-Limited by federal law to investigational use", "Caution - Radioactive material", "Do not use if cloudy or if it contains particulate matter". A sample of the label is shown below. A copy of the same label will also be affixed to the batch production record.



8.1.4 Agent Ordering and Agent Accountability

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

Sites may order agent supplies in OAOP when a patient is enrolled. Orders can be expedited overnight Monday-Thursday when the site provides courier information

8.1.4.2 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.

8.1.4.3 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.

8.1.4.4 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)
- IB Coordinator: IBCoordinator@mail.nih.gov

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Details for specimen collection, preparation and shipping will be outlined in lab manuals that will be provided to the sites.

9.1 Hypoxia Imaging Study (Required from 6 evaluable participants in the NSCLC cohort and optional for the other participants)

The hypothesis is that cediranib treatment induces tumor hypoxia detected by [^{18}F]-FMISO PET/CT imaging and that the changes in tumor hypoxia correlate with response to the combination of cediranib and olaparib.

FMISO, is a radiolabeled imaging agent that has been used for investigating tumor hypoxia with positron emission tomography (PET). An ideal hypoxia-imaging agent should distribute independently of blood flow, which is best achieved when the partition coefficient of the tracer is close to unity. Under these circumstances, imaging can be done at a time when the intracellular tracer distribution has equilibrated with the tracer in plasma near the cells. FMISO is an azomycin-based hypoxic cell sensitizer that has a nearly ideal partition coefficient and, when reduced by hypoxia, binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration, rather than by any downstream biochemical interactions.

In the clinic, [^{18}F]-FMISO has been shown to detect hypoxia in a variety of tumor types from soft-tissue sarcoma, H&N cancer, non-small cell lung cancer, breast cancer, and brain tumors [71, 77, 83-86]. For more detail, please see Section 2.4 of this protocol.

In our study, [^{18}F]-FMISO PET/CT scans will be performed at baseline and following cediranib monotherapy in the NSCLC cohort. Six evaluable patients with NSCLC will undergo 2 [^{18}F]-FMISO_PET/CT scans of the thorax. The first baseline scan will be obtained after the biopsy, the second scan will be acquired after cediranib monotherapy.

See the Study Calendar for the timing of FMISO scans and biopsies. The interval between the first baseline biopsy and the baseline scan will be less than 48 hours. The interval

between the second scan and the second biopsy will be also less than 48 hours. The cediranib exposure will be 3 once-daily doses of cediranib 30mg. In a case of major scheduling conflict an exception may be given after consulting with a P.I. that the second FMISO scan may be done on Study Day 4 after 4 once-daily doses of cediranib 30mg.

Each dynamic [^{18}F]FMISO PET scan consists of 3 parts and a CT will be performed before each part for attenuation correction. PET scans will be acquired from 0-120mins, 150-180mins, and 210-240 mins post IV automated injection of a 4-5 mCi bolus of [^{18}F]FMISO. Alternatively, a short protocol of dynamic FMISO PET scans could be acquired from 0-60 min and 90-120 min. PET/CT scans will be performed on the Siemens Biograph mCT PET/CT scanner at Yale PET center or other similar PET scanners at other institutions. An intravenous line will be placed for venous blood sampling at pre-determined times to provide an accurate value of the [^{18}F]FMISO activity input function.

Imaging Analysis: Tumor regions will be defined from the CT and PET images. A number of quantification measures will be used to compare pre- and post-drug hypoxia levels, including standardized uptake values (SUV), hypoxic volumes (HV), as well as tracer compartment kinetic modeling measures. Tumor to blood ratio (TBR) is defined as the ratio of the [^{18}F]FMISO signal in each tumor voxel in the tumor region of interest (ROI) summed from 210-240 min or 90-120 min (from short protocol) to the average signal in heart over the same time frame post-injection. Threshold values used to define HVs by [^{18}F]FMISO imaging impact the reliability and robustness of hypoxia quantification. Using a defined TBR threshold >1.2, HV percentages (fraction of tumor that is hypoxic) will be calculated based on absolute tumor volume defined by CT [131]. (Cheng J. *J Nucl Med.* 2013)

Image Interpretation:
The summed [^{18}F]FMISO imaging will be interpreted by experienced nuclear medicine physician visually, using a scoring system according to Rischin et al. (J Clin Oncol. 2006;24:2098–2104). This scoring system has 5 classes: 0=uptake less than background; 1=no regions of focal uptake greater than background; 2 = focal uptake mildly greater than background; 3=focal uptake moderately greater than background; and 4=focal uptake markedly greater than background. In a second step, these 5 classes will be grouped into 2 classes and a score ≥ 2 is considered positive for hypoxia.

TBR and HV imaging (TBR>1.2) will be generated and reviewed as well. HV will be calculated based on absolute tumor volume defined by CT.

The interpretation will be done centrally by Yale investigators. The FMISO imaging must mailed to Dr. Ming-Kai Chen at the following address **within 1 week** of completing a pair of FMISO PET/CT scans:

Positron Emission Tomography (PET) Center
Yale University
801 Howard Avenue
PO Box 208048

New Haven, CT 06520-8048
Ph: (203) 737-YPET
Fax: (203) 785-3107
Email: ming-kai.chen@yale.edu

The CT of the FMISO will not be used for disease assessment.

9.2 Integral Correlative Study

None

9.3 Integrated Correlative Studies

9.3.1 BROCA Panel – Integrated Laboratory Correlative Study

9.3.1.1 Introduction

To assess correlation of response and effect of homologous recombination deficiency (HRD) status, the BROCA-HR assay, established by the Swisher laboratory will be applied. In addition to testing the tumors, a blood sample will be obtained at baseline for germline BROCA testing. Somatic BROCA testing will be done using the baseline tumor biopsy tissue in all the disease cohorts.

One hypothesis for responses to a PARP inhibitors, is that cancer cells need to be deficient in Homologous Repair (HR) but also proficient in the alternative error prone non-homologous end joining (NHEJ) DNA repair pathway [118, 119]. Thus, loss of HR is not, by itself, sufficient for sensitivity to a PARP inhibitor, and an accurate predictor of responsiveness could require assessment of many components of both the HR and 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 [120-122]. This genomic scar could serve as a downstream functional output to measure DNA repair capacity, indicative of both HR deficiency and NHEJ proficiency. Therefore, mutations in NHEJ and other pathways that could affect HR as well as genomic scarring will also be evaluated as exploratory biomarkers. The BROCA-HR panel will be applied to the tumor samples from all the disease cohorts as integrated biomarker to evaluate if "genomic scaring" can potentially predict outcome of the combination therapy cediranib/ olaparib, and if a correlation to the hypoxia markers that are the focus of the study, can be observed. For more detail, please see Section 2.4 of this protocol.

9.3.1.2 Laboratory Testing BROCA-HR

DNA will be extracted from PBMCs and FFPE archived 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)[137]. 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 [138, 139]. 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[139, 140]. 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.

9.3.1.3 Collection, Handling and Shipping of Specimens

Details for specimen collection, preparation and shipping will be outlined in a lab manual that will be provided to the sites.

In short, tumor samples will be collected at each study site. Slides with cut tumor sections will be shipped from the participating site to Dr. Swisher's lab at University of Washington for the analyses described in this section. In addition, a 7ml blood sample is required for the germline sequencing, which will be shipped to Dr. Swisher's lab directly.

9.3.1.4 **Site Performing Correlative Study**

Dr. Elizabeth M. Swisher, MD
University of Washington
1959 NE Pacific St
Health Sciences Building K154
Seattle, Washington 98195-6460
Phone: 206-543-3669
swishere@uw.edu

9.4 Exploratory/Ancillary Correlative Studies

9.4.1 Angiome Panel (Required in all study participants)

9.4.1.1 Introduction

VEGF increases on treatment with VEGF signaling inhibitors have been observed across multiple studies with cediranib and other VEGF signaling inhibitors. VEGF is regulated by hypoxia and will serve as a well established marker for hypoxia [61, 141-143]. VEGF levels will be measured at multiple timepoints, baseline, on cediranib monotherapy, on combination therapy, and at the end of the study. Additional biomarkers for angiogenesis will be measured in parrallel. The laboratory of Dr. Andrew Nixon has established a panel of angiogenic and inflammatory markers that can be measured in plasma from patients in a multiplexed ELISA format. All samples will be assessed at Duke University Medical Center. All but one of the markers will be analyzed using the CiraScan system, produced by Aushon Biosystems. The remaining marker, TGFβRIII, will be analyzed using standard ELISA reagents from R&D Biosystems (Minneapolis, MN). The assays are designed as sandwich ELISAs and samples (patient plasma) or standards are added which bind to the specific capture antibodies and are detected using various outputs. Each commercial vendor provides calibrators or standards. Soluble TGFβRIII will be detected using a Biotek ELx808IU-PC Absorbance Microplate Reader, while all other markers will be detected using the Aushon CiraScan Imaging and Analysis system. All data collected will be quantitative with a continuous distribution of data across the range tested. For more detail, please see Section 2.4 of this protocol.

9.4.1.2 Collection, Handling and Shipping of Specimens

Details for specimen collection, preparation and shipping will be outlined in a lab manual that will be provided to the sites.
In brief, blood samples will be collected at each site, and samples must be processed within one hour of collection. For plasma samples, blood will be drawn into 10 ml purple top (K2EDTA) tubes and processed to obtain plasma as per lab manual. Plasma should be dispensed into cryovials in 1mL aliquots, and frozen at -80^{o}C until shipping. As plasma samples are analyzed in a retrospective manner, samples should be stored at the sites at -80°C and shipped in batches at a later time to be agreed with the analyzing laboratory.

9.4.1.3 Site Performing Correlative Study

Phase I Biomarker Laboratory
Andrew Nixon, PhD
Duke University Medical Center
395 MSRB, Research Drive
Durham, NC 27710

Phone: (919) 681-2239
andrew.nixon@duke.edu

9.4.2 Plasma circulating tumor DNA (Required in all study participants)

9.4.2.1 Introduction

For many types of cancer, serum protein biomarkers to monitor therapeutic efficacy either do not exist or are not very robust. For example, there are currently no blood biomarkers that are in routine clinical use to track response to therapy in patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). In patients with advanced breast and pancreatic cancers, the blood markers CA 27.29, CEA, and CA 19-9 can be used to monitor treatment response and to detect disease progression. However, these markers suffer from lack of cancer specificity, as serum levels can be elevated in patients with other types of cancer and can also be elevated in non-malignant conditions such as cirrhosis, inflammatory bowel disease, hepatitis, and renal impairment, among others. Moreover, serum levels of protein markers typically change gradually, making it difficult to obtain a rapid assessment of the effectiveness of a therapy. Thus, new blood biomarkers with greater specificity and faster response kinetics could provide a more reliable and rapid assessment of treatment efficacy to guide therapeutic decision-making.

Recent technological advances have made it possible to detect and quantify small amounts of cell-free tumor-derived DNA fragments in the bloodstream of patients with various types of cancer [97-102]. Such circulating tumor DNA (ctDNA) is believed to be released from dying cancer cells, and is showing excellent promise as a cancer biomarker [103, 104]. Tumor-derived DNA can be distinguished from normal background cell-free DNA in plasma based on the presence of tumor-specific somatic mutations. Because somatic mutations are a hallmark of cancer, circulating tumor DNA should in principle be identifiable in all types of malignancies. False-positive results are expected to be extremely uncommon since cancer-associated mutations should rarely be found in plasma in the absence of malignancy. Furthermore, because there is no physiologic background level, a small amount of mutant DNA released from a small tumor should be detectable if the technical background (error rate) of the assay can be minimized. It has also been observed (in our lab and by others) that ctDNA exhibits much more rapid posttreatment kinetics than protein markers. Most protein markers typically show a decline with successful therapy over several months, whereas ctDNA can show a dramatic decline within **~2-3 weeks** [102]. While most protein markers are secreted by living and growing cancer cells, ctDNA is a byproduct of dying cancer cells, and it is rapidly cleared from the blood with a half-life of ~2 hours [105]. Thus, ctDNA provides a real-time estimation of active tumor cell death, rather than simply a measure of tumor burden. In several cases, we have observed an initial spike in ctDNA levels within the first few days after beginning treatment (likely due to tumor kill), followed by a substantial decline below pre-treatment levels after the initial wave of cell death has subsided. This can lead to an exaggerated difference between pre- and post-treatment levels, suggesting that ctDNA may be a more responsive marker of therapeutic efficacy.

Patel laboratory has developed an ultrasensitive assay for measuring small amounts of cell-free mutant DNA released into the blood from dying tumor cells[102, 106]. The assay uses next-generation sequencing combined with novel error suppression techniques

to enable measurement of rare mutant ctDNA down to a fractional abundance of ~0.02%. Coverage of a broad panel of mutation-prone genomic regions ensures that ctDNA can be detected in the majority of patients with common solid malignancies. The assay has been tested on over 1500 clinical samples thus far. Indeed, in patients receiving chemotherapy, targeted therapy, surgery, or radiation therapy, we have observed that ctDNA levels usually decrease substantially during successful treatment (sometimes with a transient spike due to tumor kill). However, longitudinal testing of the assay has been performed mostly on heterogeneous populations of patients who were treated with a variety of regimens. To more rigorously evaluate the performance of the assay, here we plan to obtain blood samples at well-defined intervals from a population of patients having 4 different types of cancer, all receiving uniform treatment in the setting of a clinical trial. For more detail, please see Section 2.4 of this protocol.

9.4.2.2 Collection, Handling and Shipping of Specimens

Details for specimen collection, preparation and shipping will be outlined in a lab manual that will be provided to the sites.
In brief, plasma should be collected in 10 mL purple-top EDTA-containing vacutainer tubes and gently turned end over end 3-4 times upon collection to dissolve the EDTA and prevent coagulation. Tubes can then be kept at room temperature, and should be centrifuged at 1000 x g for 10 minutes in a clinical centrifuge within 4 hours of collection (sooner is better). Tubes should be carefully balanced in the centrifuge to avoid vibrations which might disrupt WBCs. The centrifuge should be stopped in "brake off" mode.

Plasma should be dispensed into cryovials in 1mL aliquots, and frozen at -80^{o}C. Care should be taken to avoid the buffy coat by not pipetting the last 5mm of plasma above the buffy coat layer. Once the plasma is frozen, it should not be thawed until it is ready to be processed for sequencing.

As plasma samples are analyzed in a retrospective manner, samples should be stored at collection sites shipped in batches at a later time to be agreed upon with the analyzing laboratory.

9.4.2.3 Site Performing Correlative Study

Laboratory of Dr. Abhijit Patel
Department of Therapeutic Radiology
Yale School of Medicine
15 York Street
Room HRT 213C
New Haven, CT 06510
Abhijit.Patel@yale.edu

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. Holding the study medication(s) or not taking the study medications prior to research samples collection or safety assessment is not considered a study deviation. The study Day continues to roll along with calendar day even in the days of dose interruptions.

			Cycle (C) 1 **(D1-35)**						Cycle 2 **(D1-28)**		C3 and later **(D1-28)**		End of Treatment
	Day (D) -30 to -1	D -2 to 0	D1	D2	D3	D 4 to 7	D8 +/- 3 ds	D15 +/- 3 ds	D1 +/- 3 ds	D15 +/- 3 ds	D1 +/- 3 ds	D15+ /- 3 ds	
Cediranib			X	X	X	X	X---------->						
Olaparib						X[1]	X ---------->						
Home BP monitoring [2]			X ---------->										
Informed Consent	X												
Registration	X												
Biopsies[3]		X[4]											
FMISO[5]		X[6]			X[6]								
Archival Tissue submission (**optional**)[3A]	X												
Research blood for **germline BROCA** testing[7]		X											
Research Blood (Angiome panel)[8]		X[9]				X[10]		X[11]	X[11]		X[11]		X
Research blood (ctDNA) [8]		X[9]				X[10]		X[11]	X[11]		X[11]		X
RECIST v1.1 Tumor Assessment	X										X[12]		X[16]
Brain MRI [13]	X												
H&PE, VS, PS, Conc Meds, Toxicity Assessment	X	X					X	X	X	X	X	X	X
Height	X												
Weight	X	X						X	X	X	X	X	X

Serum Chemistry[14], CBC w/diff, Urine Protein/Creatinine	X	X					X	X	X	X	X	X	X
			Cycle (C) 1 **(D1-35)**						Cycle 2 (**D1-28**)		C3 and later		End of Treatment
	Day (D) -30 to -2	D -2 to 0[18]	D1	D2	D3	D 4 to 7	D8 +/- 3 ds	D15 +/- 3 ds	D1 +/- 3 ds	D15 +/- 3 ds	D1+/- 3 d	D15+/- 3 ds	
INR and PTT	X	X											
TSH and free T4[15]	X												
ECHO and abdominal US (if indicated)[17]	X												
Urine Pregnancy Test[15]	X	X											

FOOTNOTES: ****** NOTE Cycle 1 has 35 days. Cycle 2 and subsequent cycles have 28 days ******

1: For patients undergoing FMISO scans, olaparib starts after the pre-dose research labs are collected, on the day after the second FMISO scan.
For the rest of the study patients, olaparib dosing starts on Day 4 (preferred) after the pre-dose research labs are collected. In case of scheduling conflicts, olaparib may start on any day between 4 and 7.

2: Patients must be advised to monitor home blood pressure twice a day for at least one week. Once deemed stable, then it may be reduced to once a day. Should further hypertension arise, return to twice daily monitoring, until at least one week of stability then can return to daily.

3: **Mandatory** for all study patients except those who can provide an archival tissue collected within the 3 months prior to the registration with no interval systemic therapy. The exception must be discussed with the study PI.

3A: If a subject is not undergoing a research baseline biopsy, archival tissue submission should be done within the first 8 weeks of the study. For the subjects who are opting in to provide additional archival tissue submission, it may be done at any time after discussing with the study PI.

4: The baseline biopsy should be obtained on either Day -2 or Day -1 **before** the baseline FMISO PET/CT scan (Day 0). For those not getting FMISO scans, the baseline biopsy should be obtained on either Day -2 or Day -1. At least one day (Day 0) must pass after the biopsy before the start of C1D1 cediranib.

5: **Mandatory** for 6 evaluable NSCLC patients. For the rest of NSLCL patients, it would be optional and highly encouraged when a participating site has funding.

6: Baseline FMISO scan should be done on Day 0 after the baseline biopsy (Day -1 or Day -2). The second FMISO scan should be done after 3 daily doses of cediranib on Day 3. In case of a major scheduling conflict, the second FMISO scan may be done on Day 4 after the 4th daily dose after discussing with the Study P.I.

7: Research blood for germline BROCA testing is necessary complete BROCA testing. Therefore, it is mandatory for those who are getting biopsy or those submitting archival tissue for somatic BROCA testing. Preferably, it should be collected along with the baseline research labs.

8: **Mandatory** for all study patients.

9: Baseline research blood samples should be collected on the day of, prior to the biopsy.

10: The second research blood samples should be collected on the day of olaparib add-in before the dosing of the study drugs (cediranib and olaparib) (See footnote 1 above).

11: All the subsequent blood samples should be collected before the dosing of the study drugs.

12: Restaging scans should be done within 7 days before or on Day 1 of cycles 3, 5, 7, 10 and every 3rd cycle thereafter, or earlier if clinically indicated.

13: Screening Brain MRI is required for NSCLC, TNBC and SCLC. For PDAC, Brain MRI is required only if clinically indicated. CT Head/Brain is acceptable if MRI is contraindicated.
14: Na, K, Chloride, Bicarbonate, BUN, Cr, Glucose, Calcium, Phosphorus, Magnesium, Albumin, Total Protein, Alkaline Phos, ALT, AST, Total Bilirubin.
15: Mandatory at baseline. Encouraged to monitor during treatment at the discretion of the treating physician.
16: The restaging scans at the EOT should be done only if clinically indicated especially for the subjects who are coming off treatment due to reasons other than disease progression.
17: Echocardiogram is indicated at screening only if inclusion 3.1.12 is applicable, and after every 4 cycles while on study if Section 6.5 is applicable, and anytime during the study if clinically indicated. Abdominal US is indicated only if exclusion 3.2.15 is applicable and anytime during the study if clinically indicated.

11. MEASUREMENT OF EFFECT

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 6-*8* (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 monotherapy-lead-in, cediranib in combination with olaparib, or FMISO infusion.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression, or unequivocal clinical progression prior to the end of cycle 1 will also be considered evaluable. Patients who failed to start the cycle 1 day 1 treatment will be considered not 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 are not be considered measurable unless the irradiated demonstrated showed radiographic progression on previous scans.

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.

The investigators should use CT scans at diagnostic quality for restaging. In order to use

PET/CT for staging, CT has to be in diagnostic quality (with oral and intravenous contrast).It will only be used for restaging only if it was used for the baseline screening.

In the setting of CT contrast is contraindicated (e.g., steroid refractory of contrast allergy, or renal insufficiency). MR of abdomen and pelvis with gadolinium, and CT Chest without contrast will be acceptable.

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

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

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

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If

the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

11.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-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.
** Confirmation is required for response.
*** In exceptional circumstances, unequivocal progression in non-target lesions may beaccepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be

reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

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

11.1.7 Response Review

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

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal. During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

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

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

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://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.

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. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. 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.

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

12.3 CTEP Multicenter Guidelines

Not Applicable

12.4 Collaborative Agreements Language

The agents 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 (hereinafter referred to as "Collaborator") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

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

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

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

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

12.5 Safety Monitoring

The site investigators will meet by teleconference at a monthly frequency for approximately 30 minutes. The site investigator(s) and research staff involved with the conduct of the protocol are required to attend. During the monthly teleconference, the investigators will discuss:

- Safety of protocol participants (AEs and reporting).
- Validity and integrity of the data (data completeness on case report forms and complete source documentation)
- Enrollment rate relative to expectation of target accrual (eligible and ineligible participants)
- Retention of participants, adherence to the protocol, and protocol violations
- Protocol amendments

12.6 Data Safety Monitoring Plan

Each participating site will provide the primary oversight of data and safety monitoring in accordance with the enrolling institution's data safety monitoring plan. The summary DSMC report from each site should be provided to the Study PI whenever it is generated.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is an open-label, multi-cohort, phase II trial of cediranib plus olaparib in patients with advanced solid tumors of the following histopathology: NSCLC, TNBC, PDAC and SCLC. The study utilizes a Simon 2-stage design to assess anti-tumor activity of the combination therapy in each of these disease cohorts running in parallel.

Of note, the NSCLC, PDAC and SCLC cohorts uses the minimax design whereas basaloid TNBC and non-basaloid TNBC cohorts use the optimal design. The rationale for the minimax design for the NSCLC, PDAC and SCLC is because the combination therapy has never been tested in these tumor types. The minimax design allows the maximal number of patients during the stage 1 before the study may get terminated for futility. The optimal design was chosen for TNBC because the combination has been previously tested in TNBC patients in a small phase I study by Joyce Liu et al. (Eur J. Cancer 2013.) While not definitive conclusion, the study suggested rather inactivity of the combination regimen in patients with TNBC. Therefore, optimal design was chosen to keep the exposure of the investigational regimen at minimum for TNBC patients during the stage 1 before terminating the study for futility.

Primary endpoint

- The objective response rate (ORR) in each of the cohorts. The responses will be assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The ORR is defined by the total number of patients with either complete response or partial response divided by the total number of patients evaluable per response assessment. For best overall response, confirmation of response is required by the subsequent scans $\geq$ 4 weeks apart.

Secondary endpoints

- Safety as measured by the risk of adverse events per NCI CTCAE v5.0. All subjects who receive at least a dose of study medications will be included for safety analysis.

- Progression free survival (PFS): PFS is defined as the duration of time from start of treatment to time of disease progression or death, whichever occurs first. Subjects who remain alive and have not progressed or received new therapy will be censored on the date of last protocol specified tumor assessment.

Exploratory endpoints:

- Prevalence of the mutations of DNA repair genes in each tumor cohort.
- Changes in tumor hypoxia by imaging, as measured by FMISO PET/CT scans at pre- and post-cediranib monotherapy. (NSCLC cohort)
  a) clinically relevant Hypoxic volume (HV) post cediranib based on tumor-blood ratio (TBR) > 1.2.
  b) score ≥ 2 post cediranib based on visual interpretation with 5-point scoring system.
- Changes in level of circulating tumor DNA at pre- and post cediranib monotherapy and on combination therapy. (All cohorts)
- Changes in levels of angiogenesis/ inflammatory markers (angiome panel) at pre- and post cediranib monotherapy and on combination therapy. (All cohorts)

NSCLC and PDAC cohorts:

A Simon (Minimax) two-stage design is utilized to develop interim analysis guidelines to evaluate if there is "minimal activity" to fully enroll the current study and to consider cediranib plus olaparib in combination for study in future trials. If there is evidence that the true underlying overall ORR is at least 20%, consideration will be given for further testing of cediranib plus olaparib in combination. However, if cediranib plus olaparib in combination is inactive in NSCLC, PDAC or TNBC patients, then the study should be terminated early. Initially, 18 eligible patients will be entered into the study. If there is less than 1 response in these first 18 patients, the trial will be terminated. If there are at least one or more than one responses in these first 18 patients, the trial will continue until 32 patients have been treated. If there are less than 4 responses in these 32 patients then the study will be terminated, otherwise a phase III study will be conducted in the future. This design provides 90% statistical power to detect a difference of 15% (20% vs. 5%) with a significance level less than 0.1 (type I error).

TNBC cohort:

A Simon (Optimal) two-stage design is utilized to develop interim analysis guidelines to evaluate if there is "minimal activity" to fully enroll the current study and to consider cediranib plus olaparib in combination for study in future trials. If there is evidence that the true underlying overall ORR is at least 20%, consideration will be given for further testing of cediranib plus olaparib in combination. However, if cediranib plus olaparib in combination is inactive in TNBC patients, then the study should be terminated early. Initially, 12 eligible patients will be entered into the study. If there is less than 1 response in these first 12 patients, the trial will be terminated. If there are at least one or more than one responses in these first 12 patients, the trial will continue until 37 patients have been treated. If there are less than 4 responses in these 37 patients then the study will be terminated, otherwise a phase III study will be conducted in the future. This design provides 90% statistical power to detect a difference of 15% (20% vs. 5%) with a significance level less than 0.1 (type I error).

SCLC Cohort:

A Simon (Minimax) two-stage design described above is applied to the sample size estimation for this cohort. If there is evidence that the true underlying overall ORR is at least 30%, consideration will be given for further testing of cediranib plus olaparib in combination. However, if cediranib plus olaparib in combination is inactive in SCLC patients, then the study should be terminated early. Initially, 16 eligible patients will be entered into the study. If there are less than 2 responses in these first 16 patients, the trial will be terminated. If there are two or more responses in these first 16 patients, the trial will continue until 25 patients have been treated. If there are less than 5 responses in these 25 patients then the study will be terminated, otherwise a phase III study will be conducted in the future. This design provides 90% statistical power to detect a difference of 20% (30% vs. 10%) with a significance level less than 0.1 (type I error).

NOTE: Subjects who are not considered evaluable for objective response as defined in 11.1.1 will be replaced.

13.2 Sample Size/Accrual Rate

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	2	1	2	1	**6**
Asian	3	3	3	3	**12**
Native Hawaiian or Other Pacific Islander	2	2	2	1	**7**
Black or African American	**13**	**4**	**8**	**4**	**29**
White	**11**	**7**	**11**	**7**	**36**
More Than One Race	**11**	7	11	7	**36**
Total	**42**	**24**	**37**	**23**	**126**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

13.3 Stratification Factors

Not applicable

13.4 Analysis of Study Endpoints

Statistical Analysis Plan:

The effectiveness of the cediranib plus olaparib in combination in patients will be assessed by overall response rate (ORR). The exact two-sided 95% confidence interval for the ORR will be reported.

For lifetime data analyses, e.g., PFS, the study progression free survival will be estimated using the Kaplan-Meier method with the 95% confidence intervals (CIs). Thomas and Grunkemeier CI which was derived by minimizing the likelihood function under certain constraints will be reported. In addition, the possible risk factors such as stage and performance status, will be compared for survival with log-rank test. For multivariate analysis, the proportional hazards Cox model will be applied to investigate potential prognostic factors, such as age and stage of disease on the survival data. The adjusted p-values of the hazard ratios and the adjusted 95% confidence interval will be reported.

Statistical Plan for the Imaging Endpoint:
With our 6 FMISO-evaluable patients with NSCLC, we will use descriptive statistical analyses such as paired t-test and Wilcoxon Sign Rank test, to compare [18F]-FMISO binding for the primary measure of tumor to blood ratio (TBR) and hypoxia volume (HV) for differences in tumor hypoxia within subjects and individual target tumors (up to 5 targets per subject) before and after cediranib treatment. We will use McNemar's test to evaluate the categorical scores before and after cediranib within subjects.

Other Exploratory Endpoints:
In our first 20 endpoint-evaluable patients with NSCLC and 20 endpoint-evaluable patients with TNBC, the exploratory analyses will be done using Fisher's exact tests, Mann-Whitney U tests or McNemar's test will be applied depending the type of data we observe. For the pre- and post-cediranib therapy outcome analysis, paired t- test or Wilcoxon signed-rank will be applied for the continuous variables. McNemar's test will be applied for categorical variables. Fisher's exact test will be applied for the association between hypoxia positivity and objective response. We will use these information from to estimate the 95% confidence intervals for future pivotal trials.

Analysis Plan for Safety Data:
Safety will be measured by the risk of adverse events per NCI CTCAE v5.0. All subjects who receive 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. The PK parameters will be presented in the table and figure format.

Sensitivity Analysis for Protocol Violations:

The sensitivity analyses will be performed to evaluate the study results excluding patients having a major protocol violation.

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 monotherapy-lead-in, cediranib in combination with olaparib, or FMISO infusion.

The following AEs categories will be reported separately:

- The AEs observed with cediranib monotherapy.
- The AEs observed with FMISO infusion during the study.
- The AEs observed with cediranib in combination with olaparib.

13.5.2 Evaluation of Response

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

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

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

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B: NEW YORK HEART ASSOCIATION CLASSIFICATIONS

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

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

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

** At accustomed occupation or usual tasks

APPENDIX C 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 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 Inhibitors** of CYP3A are prohibited

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 Inducers** of CYP3A are prohibited.

APPENDIX D PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **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 _____.

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 E: PILL DIARIES AND BLOOD PRESSURE MONITORING FOR CYCLE 1 (DAYS 1 THRU 35)
Today's Date _____ Cycle # **1**
Patient Name _____ Patient Study ID _____

1. Complete one form for each cycle.
2. Record the date, the number of tablets you took, and when you took them.
3. Bring your pill bottles (including empty bottles) and this form to every appointment.
4. Do not chew, dissolve, or crush medications. DO NOT make up vomited doses.
5. If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose.

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

CEDIRANIB Take ____ (number) _____ mg tablets once a day every 24 hours. Take on an empty stomach 1 hour before taking the morning dose of olaparib.					**OLAPARIB** Take _____ (number) _____ mg tablets twice a day 12 hours apart with a light meal. You should avoid grapefruit juice while on study because grapefruit juice affects the metabolism of olaparib. The morning dose should be taken approximately 1 hour after cediranib, with a light meal.						**Blood Pressures** Call your study team if your BP is greater than 140/90 !!		**BP Medications**
Day	**Date**	**15mg**	**20mg**	**AM**	**Day**	**Date**	**100mg**	**150mg**	**AM**	**PM**	**AM**	**PM**	
1	*1/1/15*	*2*	*0*	*7:00*	*1*	*1/1/15*	*2*	*0*	*7:00*	*7:00*	*112/62*	*121/68*	
1					1						/	/	
2					2						/	/	
3					3						/	/	
4					4						/	/	
5					5						/	/	
6					6						/	/	
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32					32								
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34					34								
35					35								
Patient's Signature: _____ Date: _____ Physician/Nurse/Data Manager's Signature _____ Date_____													

APPENDIX F: PILL DIARIES AND BLOOD PRESSURE MONITORING FOR CYCLE 2 AND LATER (DAY 1 THRU 28)
Today's Date _____ Cycle # _____
Patient Name _____ Patient Study ID _____

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

CEDIRANIB Take ____ (number) _____ mg tablets once a day every 24 hours. Take on an empty stomach 1 hour before taking the morning dose of olaparib.					**OLAPARIB** Take _____ (number) _____ mg tablets twice a day 12 hours apart with a light meal. You should avoid grapefruit juice while on study because grapefruit juice affects the metabolism of olaparib. The morning dose should be taken approximately 1 hour after cediranib, with a light meal.						**Blood Pressures** Call your study team if your BP is greater than 140/90 !!		**BP Medications**
Day	**Date**	**15mg**	**20mg**	**AM**	**Day**	**Date**	**100mg**	**150mg**	**AM**	**PM**	**AM**	**PM**	
1	*1/1/15*	*2*	*0*	*7:00*	*1*	*1/1/15*	*2*	*0*	*7:00*	*7:00*	*/*	*/*	
1					1						/	/	
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3					3						/	/	
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28					28						/	/	
Patient's Signature: _____ Date: _____ Physician/Nurse/Data Manager's Signature _____ Date_____													

APPENDIX G: ORAL ANTIHYPERTENSIVE MEDICATIONS

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

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

β Blockers (BB)	**atenolol**	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	CYP 3A4 substrate
α and β Blocker	labetalol	100 mg twice daily	200 mg twice daily	400 mg twice daily	Yes, but not CYP450
Diuretics	Hydralazine	10 mg four times daily	25 mg four times daily	50 mg four times daily	no
	Hydrochlorothiazide	12.5 mg AM daily	25 mg AM daily	50 mg AM daily	no
	Furosemide	20 mg daily	20 mg twice daily	40 mg twice daily	no
Nitrates	Isosorbide dinitrate ER	40 mg daily	40 mg twice daily	80 mg twice daily	CYP 3A4 substrate
	Isosorbide mononitrate ER	30 mg AM daily	60 mg AM daily	90 mg AM daily	CYP 3A4 substrate
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: LAB MANUAL

NCI Protocol 9881 LABORATORY MANUAL

Inserted into the Protocol

A Phase 2 Study of Cediranib in Combination with Olaparib in Advanced Solid Tumors

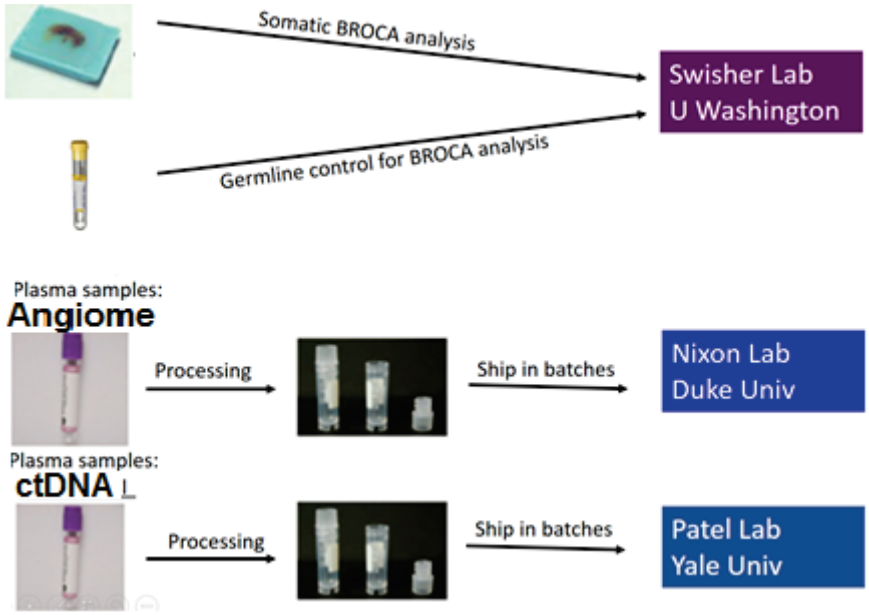
Study Sponsor: **NCI**
PI: **Joseph W. Kim, MD, Yale University**
Translational Lead: **J. Paul Eder, MD Yale University**

1. INTRODUCTION

This manual covers the procedures associated with acquisition of patient samples for biomarker analysis, processing, storage and shipment of these samples to central laboratories as required by the protocol.

2. SAMPLE FLOW OVERVIEW

Tumor tissue, blood and plasma biomarker samples will be collected and sent to central laboratories for storage and analysis. The diagram below highlights the flow process for all lab samples.



3. SAMPLING TIME POINTS

3.1 Tumor Tissue Samples

Baseline tumor tissue samples will be obtained from **all** study patients. Samples will be used to determine the molecular profile (deoxyribonucleic acid; DNA) of patient's tumor and in particular the homologues recombination deficiency (HRD)-status of the tumors, compared to the normal cells (see blood sample below).

Cycle and Day	Time
Day -2 to 0	The baseline biopsy will be done after the research blood draws are collected. (See section 4.1 for submission of FFPE blocks from biopsy)

Any day on study	Archival tumor tissue submission (optional) (See section 4.5 for submission of archival tumor tissue)

3.2 Blood samples

Blood samples will be obtained from all study patients who are undergoing biopsies or submitting an archival tissue for BROCA testing. Samples will be used to determine the germline molecular profile of patients, compared to the tumor (see tumor sample above).

Cycle and Day	NOTE
See the 3.1 (same time as the tumor tissue submission)	Any patients who are undergoing biopsy or submitting archival tissue for BROCA testing, must be accompanied by this germline testing by submitting a blood sample.

3.3 Plasma (for markers of angiogenesis and inflammation) Collection Time Points

Plasma samples to assess markers of angiogenesis and inflammation will be collected at the following time points:

Cycle and Day	Time
Baseline, Day -2 to 0	On the day of the biopsy, before the biopsy is performed.
Cycle 1, Day 4-7	On the day of the biopsy. The sample will be drawn **before the first dose of olaparib.**
Cycle 1 Day 15 +/- 3 days	before dosing
Cycle 2 and the subsequent cycles, Day 1 +/- 3 days	before dosing
End of treatment: Discontinuation	After discontinuation of the therapy.

3.4 Plasma (for ctDNA) Collection Time Points

Plasma samples will be collected to isolate ctDNAs as markers of hypoxia:

Cycle and Day	Time

Baseline, Day -2 to 0	On the day of the biopsy, before the biopsy is performed.
Cycle 1, Day 4-7	On the day of the biopsy. The sample will be drawn **before the first dose of olaparib.**
Cycle 1 Day 15 +/- 3 days	before dosing
Cycle 2 and the subsequent cycles, Day 1 +/- 3 days	before dosing
End of treatment: Discontinuation	After discontinuation of the therapy.

4 SAMPLE COLLECTION AND PROCESSING PROCEDURES

All lab supplies, including collection tubes and cryovials, labels, and shipping containers, will need to be provided by each site.

4.1 Tumor biopsy tissue samples

- Samples should be taken either by incisional biopsy or by core needle biopsy (14 gauge) according to each institution's standards. If possible 3 to 5 samples per patient and time point should be acquired. (***The samples not meeting this requirement may be acceptable, but MUST be discussed with the Study PI or Swisher Lab***).
- The size of each tissue sample should be in the range of 3 to 5 mm.
- In order to keep time from tissue acquisition to fixation as short as possible, these samples should be placed in 10% neutral buffered formalin (NBF) within 15 minutes of the procedure.
- The samples should be kept in 10% NBF for a duration of at least 6 hours and no longer than 72 hours.
- Following formalin fixation, tissue samples should be paraffin embedded according to established in house protocols at the sites.
- Paraffin embedded samples should be placed into cassettes and labeled on the cassette with a normal pencil with the following information:

  1. Protocol Name
  2. Subject Study Number
  3. Sample Date and Time

- Each tissue core should be placed in a separate block resulting in 3-5 paraffin blocks per initial biopsy per patient.
- Paraffin embedded tissue blocks should be stored at room temperature until shipped.
- Paraffin block should be wrapped in bubble wrap and shipped in one box together to the address provided below.
- Complete the Tumor Tissue Shipping Form (Form 1) and insert a copy of it with shipment.

- Samples should be shipped Monday through Thursday to the following laboratory:

  Swisher Lab
  University of Washington
  1959 NE Pacific St
  Health Sciences Building BB632
  Seattle, Washington 98195-6460
  Phone: 206-685-7927
  Email: ovcalab@uw.edu

4.2 **Blood Samples for germline BROCA panel**

- Required material:
  - 8.5 ml Acid Citrate Dextrose (ACD) tubes: ACD Solution A tubes: Fisher Scientific catalog # 02-684-26 for pk of 100
  - Tubes with cap (items ordered separately) to hold blood tubes: Sarstedt cat # 78.898 for 30 X 126 tube with absorbent, case of 250; and Sarstedt cat # 65.679 for cap, case of 250
  - Cardboard shipping box to hold 3 tubes: U-line cat # S-463 for 5X4X2 box, pack of 100 (tbc). If using this box for 1 sample, 2 empty plastic tubes need to be added to the plastic tube containing the blood sample.
  - Avery labels # 5160 for labelling tubes- can purchase from any office supply

- Draw 7ml of blood into one 8.5ml ml yellow top Acid Citrate Dextrose (ACD Solution A) tube on any weekday except Friday.
- Invert tube 10 times to mix blood
- Label the tubes after blood collection with the following information:

  1. Protocol Name
  2. Subject Study Number (the lab should NOT receive any patient identifiers, e.g., subject initials or date of birth)
  3. Sample Date and Time
  4. Sample Type (whole blood)

- *Complete the Blood Sample Shipping Form (germline control for BROCA panel) (Form 2) and insert a copy of with shipment.*
- Samples should be shipped at ambient temperature for overnight delivery to the following laboratory:

  Swisher Laboratory
  University of Washington
  1959 NE Pacific St
  Health Sciences Building BB632
  Seattle, Washington 98195-6460
  Phone: 206-685-7927
  ovcalab@uw.edu

4.3 Plasma samples for Markers of Angiogenesis and Inflammation

Biomarker assays are time sensitive. Samples must be processed within one hour of collection. Complete the Biomarker shipping Form Plasma for Angiogenesis and Inflammation Markers (Form 3) 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)

- Draw blood into one 10ml lavender top (K_2EDTA) tube (BD Vacutainer, Catalog no. 366643)
- Invert tubes 10 times to mix blood
- Centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
- Remove plasma from each tube and transfer equally into two separate clean 15ml polypropylene tubes
- Repeat centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
- 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.
- Label tubes with the following information (using a Sharpie or Cryopen):

  1. Protocol Name
  2. Subject Study Number
  3. Subject Initials
  4. Sample Date and Time
  5. Sample Type (EDTA plasma)

- Vials should be frozen at -80°C immediately in an upright position and kept at -80°C until shipment.
- 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.
- Complete the Plasma Biomarker Sample Shipping Form (Angiogenesis and Inflammation Markers) (Form 3) and insert a copy of with shipment.
- 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
  ATTN: Andrew Nixon, PhD

Duke University Medical Center
395 MSRB, Research Drive
Durham, NC 27710
Phone: (919) 681-2239
Email: andrew.nixon@duke.edu

4.4 Plasma Biomarker Samples for ctDNA analysis

- Required material:
  - 10 mL purple/lavender-top EDTA-containing vacutainer tubes tubes (BD Vacutainer, Catalog no. 366643)
  - Cryovials or microfuge tubes capable of storing at least 1 mL of plasma
  - Labels designed for low temperatures (e.g., Cryo-Tag brand)

- Blood should be collected in 10 mL purple-top EDTA-containing vacutainer tubes and shipped in cryovials.
- Prepare a label with the required information (see below) using a fine point permanent marker. Apply completed labels to the K_2EDTA Vacutainer tubes and cryovials.
- Collect the maximum amount of whole blood into a single 10.0 mL lavender top K_2 EDTA Vacutainer tubes using standard venipuncture technique. Ensure that the tube is filled as much as possible. If blood is collected from a port-a-cath, standard precautions should be used to avoid sampling blood that is diluted with saline or heparin from the port line (an appropriate volume should be discarded as waste before collecting the blood).
- Gently invert the tubes, 3-4 times upon collection to dissolve the EDTA and prevent coagulation.
- Tubes can then be kept at room temperature up to 4 hours, but processing them sooner is better.
- Tubes should be centrifuged at 1000 x g for 10 minutes in a clinical centrifuge with a swinging bucket rotor. Tubes should be carefully balanced in the centrifuge to avoid vibrations which might disrupt WBCs. The centrifuge should be stopped in "brake off" mode.
- After centrifugation, use a new pipette to remove the plasma without disturbing the cell layer. Care should be taken to avoid the buffy coat by not pipetting the last 5 mm of plasma above the buffy coat layer.
- Plasma should be dispensed into cryovials in 1mL aliquots. Cap the cryovials tightly.
- *Label tubes with the following information (using a Sharpie or Cryopen):*

  1. Protocol Name
  2. Subject Study Number
  3. Subject initials
  4. Sample Date and Time
  5. Sample Type (EDTA plasma)

- Vials should be frozen at -80ºC immediately in an upright position and kept at -80ºC until shipment.
- As plasma samples are analyzed for ctDNAs 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.
- Samples collected at Yale will be hand-delivered to the analyzing laboratory in batches.
- Complete the Plasma Biomarker Sample Shipping Form (ctDNA samples) (Form 4) and insert a copy of with shipment.
- Samples should be shipped to the following laboratory on dry ice overnight:

  Attn: Azeet Narayan
  Laboratory of Dr. Abhijit Patel
  Department of Therapeutic Radiology
  Yale School of Medicine
  15 York Street
  Room HRT 213C
  New Haven, CT 06510
  Phone: 203-737-6252
  Fax: 203-785-7482
  Email: abhijit.patel@yale.edu

4.5 Archival tumor sample submission (OPTIONAL)

- Submit **three** unstained, charged slides; Two slides cut at 10 microns and one slide cut at 4 microns.
- The slides should be wrapped in bubble wrap and shipped in one box together to the address provided below.
- Complete the Tumor Tissue Shipping Form (Form 1) and insert a copy of it with shipment.
- Samples should be shipped Monday through Thursday to the following laboratory:

  Swisher Lab
  University of Washington
  1959 NE Pacific St
  Health Sciences Building BB632
  Seattle, Washington 98195-6460
  Phone: 206-685-7927
  Email: ovcalab@uw.edu

5 SAMPLE SHIPMENT PROCEDURES

5.1 Tumor Tissue Shipping

Tumor biopsies are formalin-fixed and paraffin-embedded.

- Ship Monday through Thursday. Do not ship on Friday as receiving lab cannot receive weekend samples. Agree timing of shipment with receiving laboratory.

- For every shipment, send an email notification to the receiving lab with tracking number, and attach electronic version of completed Tumor Tissue Shipping Form (see Form 1) to ovcalab@uw.edu and the study coordinator (NCI9881Specimen@yale.edu).
- Samples should be packaged carefully. Tissue blocks can be wrapped in tissue paper or bubble wrap and placed into one box for shipping.
- Blocks should be shipped at ambient temperature.
- Include a completed Tumor Tissue Shipping Form (Form 1) itemizing the contents of the shipment. A photocopy should be maintained with study records at each site.
- All samples should be shipped at ambient temperatures to the following address:

Swisher Laboratory
University of Washington
1959 NE Pacific St
Health Sciences Building BB632
Seattle, Washington 98195-6460
Phone: 206-685-7927
ovcalab@uw.edu

5.2 Blood Sample Shipping

Blood samples to determine the germline BROCA panel, need to be shipped to ensure delivery within 24 hours of collection. Instructions for packing and notifications for shipment follow:

- Specimens must be packaged according to IATA regulations for shipping UN3373, Biologic specimen category B. Each Blood tube should be placed inside a plastic Sarsted tube with absorbent. Place the Sarsted tube, including ACD blood tube in the cardboard inner box and add 2 empty Sarsted tubes as spacers. The cardboard inner box should be placed inside a Fedex UN3373 envelope (order direct from Fedex).
- Include a completed Blood Sample Shipping Form (germline control for BROCA panel) (Form 2) itemizing the contents of the shipment. A photocopy should be maintained with study records at each site. Confirm that the identifies (subject number and initials) are in agreement.
- 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 Blood Sample Shipping Form (germline control for BROCA panel) (Form 2) to ovcalab@uw.edu and the study coordinator (NCI9881Specimen@yale.edu).
- All samples must be shipped Monday through Thursday at ambient temperatures for overnight delivery to the following address:

Swisher Laboratory
University of Washington
1959 NE Pacific St
Health Sciences Building BB632

Seattle, Washington 98195-6460
Phone: 206-685-7927
Email: ovcalab@uw.edu

5.3 Plasma Sample Shipping (Markers of Angiogenesis and Inflammation)

Plasma samples should be batch shipped at times agreed with the receiving laboratory (Dr. Andrew Nixon). 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 (NCI9881Specimen@yale.edu).
- 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

5.4 Plasma Sample Shipping (ctDNA)

Plasma samples should be batch shipped at times agreed with the receiving laboratory (Dr. Abhijit Patel, Yale). Instructions for packing and notifications for shipment follow:

- Agree 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 (see Form 4) 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 Transmittal Form (Form 4) to abhijit.patel@yale.edu and the study coordinator (**NCI9881Specimen@yale.edu**).
- Samples collected at Yale should be hand-delivered in batches to the analyzing lab, using the same forms.
- All samples must be shipped on dry ice by overnight delivery Monday through Wednesday (no holidays in the same week) to the following address:

Attn: Azeet Narayan
Laboratory of Dr. Abhijit Patel
Department of Therapeutic Radiology
Yale School of Medicine
15 York Street
Room HRT 213C
New Haven, CT 06510
Phone: 203-737-6252
Email: abhijit.patel@yale.edu

5.5 General Shipping Instructions

As biomarker analyses will be performed at the end of the study, biomarker samples with the exception of the whole blood sample, that needs to be shipped freshly, should be stored at the site and shipped in batches at a time agreed with the receiving lab. All courier shipments must be made Monday to Wednesday. Do not ship samples the day before a national holiday. Shipping addresses for samples follow:

Archival tumor tissue **&** **Blood samples for germline BROCA testing**	Swisher Laboratory University of Washington 1959 NE Pacific St Health Sciences Building BB632 Seattle, Washington 98195-6460 Phone: 206-685-7927 Email: ovcalab@uw.edu
Plasma for markers of angiogenesis and inflammation	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

Plasma for ctDNA analyses	Attn: Azeet Narayan Laboratory of Dr. Abhijit Patel Department of Therapeutic Radiology Yale School of Medicine 15 York Street Room HRT 213C New Haven, CT 06510 Phone: 203-737-6252 Email: abhijit.patel@yale.edu

6 CONTACT INFORMATION

For any questions on sample collection, processing, storage and shipment, please contact the team members listed below.

Coordinator	**Yale University**	Nora Autuori Office: (203)737-1694 Mobile: (203)361-4423 Fax: (203)785-4116 Email: nora.autuori@yale.edu
Study PI	**Yale University**	Joseph W. Kim, MD Yale Cancer Center 333 Cedar Street, FMP 121 New Haven, CT 06520 Direct Office: 203-737-6467 Cell: 203-494-3287 Email: joseph.w.kim@yale.edu
Translational Science Leader	**Yale University**	J. Paul Eder, MD Yale Cancer Center 333 Cedar Street WWW 211, PO Box 208028 New Haven, CT 06520 Office: 203-737-1906 Email joseph.eder@yale.edu
BROCA Analyses	**University of Washington**	Swisher Laboratory University of Washington 1959 NE Pacific St Health Sciences Building BB632 Seattle, Washington 98195-6460 Phone: 206-685-7927 Email: ovcalab@uw.edu
Angiogenesis/ Inflammation Biomarker analyses (plasma)	**Duke University**	Phase I Biomarker Laboratory Andrew Nixon, PhD Duke University Medical Center 395 MSRB, Research Drive Durham, NC 27710 Phone: (919) 681-2239 Email: andrew.nixon@duke.edu
ctDNA analysis lab (plasma	**Yale University**	Abhijit Patel, MD, PhD Department of Therapeutic Radiology Yale School of Medicine 15 York Street Room HRT 213C New Haven, CT 06510 Phone: 203-737-6252 Email: abhijit.patel@yale.edu

7 FORMS

Form 1 Tumor Tissue Shipping Form

Form 2 Blood Sample Shipping Form (germline control for BROCA panel)

Form 3 Plasma Biomarker Sample Shipping form Angiogenesis and Inflammation Markers

Form 4 Plasma Biomarker Sample Shipping Form ctDNA

FORM 1

Tumor Tissue Shipping Form

Please copy this form for multiple shipments

Form 1: Tumor Tissue Shipping Form
Protocol CTEP/ETCTN# 9881

Shipment prepared by: (Print Name)	Site contact Phone number: Site email:	Page _____ of _____	Site: PI:

Patient ID	Tissue Type	Diagnosis	Date Collected	Sample	Number of samples per timepoint	Record time of collection for each specimen	Record time of immersion of the sample into formalin	Record duration of formalin fixation of the sample	Record storage condition of the FFPE block
				[] FFPE fresh biopsy **[] archival tumor slide**					
				[] FFPE fresh biopsy **[] archival tumor slide**					
				[] FFPE fresh biopsy **[] archival tumor slide**					

Shipping instructions:
Record the shipping date and total # of samples in shipment below. Photocopy the *Tumor Tissue Shipping Form.* The original form should accompany the shipment. Retain a copy of the form with the study documents. Email to agree shipment times in advance of shipment, then email shipment tracking number and an electronic version form of the shipment to the Swisher Lab (ovcalab@uw.edu) and the study coordinator (NCI9881Specimen@yale.edu). For details please see section 5.1 of this Laboratory Manual.

Shipping Date:	**Ship to:** Swisher Laboratory University of Washington 1959 NE Pacific St Health Sciences BuildingBB632 Seattle, Washington 98195-6460 Phone: 206-685-7927 Email: ovcalab@uw.edu
Tracking number:	
Number of samples in shipment:	

FORM 2

Blood Sample Shipping Form
(germline control for BROCA)

Please copy this form for multiple shipments

Form 2: *Blood Sample Shipping Form (germline control for BROCA panel)*

Shipment prepared by: (Print Name)	Site contact Phone number: Site email:	Page _____ of _____ **Confirm subject number and initials for each patients are in agreement (sign):**	Site: PI:
Results of the blood BROCA test will be returned to the site PI. Please add name, address, email address, phone and fax number below:			

Patient ID	**Date Collected**	**Sample**	**Number of aliquots per timepoint**	**Record time collected for each specimen**
		Baseline		

Shipping instructions:
Record the shipping date and total # of samples in shipment below. Photocopy the *Blood Sample Shipping Form*. The original form should accompany the shipment. Retain a copy of the form with the study documents. Email swishere@uw.edu to agree shipment times in advance of shipment, then email shipment tracking number and an electronic version form of the shipment to Dr. Swisher and the study coordinator (NCI9881Specimen@yale.edu). For details please see section 5.2 of this Laboratory Manual.

Shipping Date:	Number of samples in shipment:	Tracking number:
Ship to: Swisher Laboratory University of Washington 1959 NE Pacific St Health Sciences Building BB632 Seattle, Washington 98195-6460 Phone: 206-685-7927 Email: ovcalab@uw.edu		

FORM 3

Plasma Biomarker Sample Shipping Form (Angiogenesis and Inflammation Markers)

Please copy this form for multiple shipments

Form 3: Plasma Biomarker Sample Shipping Form (Angiogenesis and Inflammation Markers)

Shipment prepared by: (Print Name)	Site contact Phone number: Site email:	Page _____ of _____	Site: PI:

Shipping instructions:
All samples must be shipped overnight on dry ice. For details please see section 5.3 of this Laboratory Manual.

Patient ID	**Patient Initials**	**Date Collected**	**Sample**	**Number of aliquots per timepoint**	**Record time collected for each specimen**
			Baseline		
			Cycle 1Day 4-7		
			Cycle 1 Day 15 +/- 3 days		
			Cycle 2 Day 1 +/- 3 days		
			Cycle __ Day 1 +/- 3 days		
			EOT: Discontinuation		
Patient ID	**Patient Initials**	**Date Collected**	**Sample**	**Number of aliqots per timepoint**	**Record time collected for each specimen**
			Baseline		
			Cycle 1Day 4-7		
			Cycle 1 Day 15 +/- 3 days		
			Cycle 2 Day 1 +/- 3 days		
			Cycle __ Day 1 +/- 3 days		
			EOT: Discontinuation		
Patient ID	**Patient Initials**	**Date Collected**	**Sample**	**Number of aliqots per timepoint**	**Record time collected for each specimen**
			Baseline		
			Cycle 1Day 4-7		
			Cycle 1 Day 15 +/- 3 days		
			Cycle 2 Day 1 +/- 3 days		
			Cycle __ Day 1 +/- 3 days		
			EOT: Discontinuation		

Shipping Date:	Number of samples in shipment:	Tracking number:
Ship to: Phase I Biomarker Laboratory Andrew Nixon, PhD Duke University Medical Center 395 MSRB, Research Drive Durham, NC 27710 Phone: (919) 681-2239 Email: andrew.nixon@duke.edu		

FORM 4

Plasma Biomarker Sample Shipping Form (ctDNA samples)

Please copy this form for multiple shipments

Form 4: Plasma Biomarker Sample Shipping Form (ctDNA samples)

Shipment prepared by: (Print Name)	Site contact Phone number: Site email:	Page _____ of _____	Site: PI:

Shipping instructions:
All samples must be shipped overnight on dry ice. For details please see section 5.4 of this Laboratory Manual.

Patient ID	**Patient Initials**	**Date Collected**	**Sample**	**Number of aliquots per timepoint**	**Record time collected for each specimen**
			Baseline		
			Cycle 1Day 4-7		
			Cycle 1 Day 15 +/- 3 days		
			Cycle 2 Day 1 +/- 3 days		
			Cycle __ Day 1 +/- 3 days		
			EOT: Discontinuation		
Patient ID	**Patient Initials**	**Date Collected**	**Sample**	**Number of aliqots per timepoint**	**Record time collected for each specimen**
			Baseline		
			Cycle 1Day 4-7		
			Cycle 1 Day 15 +/- 3 days		
			Cycle 2 Day 1 +/- 3 days		
			Cycle __ Day 1 +/- 3 days		
			EOT: Discontinuation		
Patient ID	**Patient Initials**	**Date Collected**	**Sample**	**Number of aliqots per timepoint**	**Record time collected for each specimen**
			Baseline		
			Cycle 1 Day 4-7		
			Cycle 1 Day 15 +/- 3 days		
			Cycle 2 Day 1 +/- 3 days		
			Cycle __ Day 1 +/- 3 days		
			EOT: Discontinuation		

Shipping Date:	Number of samples in shipment:	Tracking number:
Ship to: Attn: Azeet Narayan Laboratory of Abhijit Patel Department of Therapeutic Radiology Yale School of Medicine 15 York Street Room HRT 213C New Haven, CT 06510 Phone: 203-737-6252 Email: abhijit.patel@yale.edu		