SUMMARY OF CHANGES - Protocol

NCI Protocol # 8348

Local Protocol # 09-293

Current Protocol Version Date: January 03, 2019

Previous Protocol Version Date: July 30, 2018

#	Section	Page(s)	Change
1.	Header; Title Page	All; 1	The protocol version date has been updated from July 30, 2018 to January 03, 2019.
2.	Title Page	2	The Site PIs for University of Michigan and Evanston Hospital/NorthShore University Health System have been updated.

3.	6.1.1	40-43	Revision of the Protocol CAEPR:
			• Added New Risk:
			  • Rare but Serious: Hemolytic uremic syndrome; Thrombotic thrombocytopenic purpura
			• Increase in Risk Attribution:
			  • Changed to Rare but Serious from Also Reported on Cediranib Trials But With Insufficient Evidence for Attribution: Heart failure; Hepatic failure; Nephrotic syndrome; Wound complication

4.	ICF – Ph 1	12	Revision of the ICD as Specified Below:
			The condensed risk profile has been modified
			• Added New Risk:
			  • Rare: Anemia, kidney problems which may cause tiredness, bruising, swelling, or may require dialysis
			• Increase in Risk Attribution
			  • Changed to Rare from Also Reported on Cediranib Trials But With Insufficient Evidence for Attribution (i.e., added to Risk Profile): Liver damage which may cause yellowing of eyes and skin, swelling; Non-healing surgical site
			• Provided Further Clarification:
			  • Blood clot which may cause swelling, pain, shortness of breath (under Occasional) is now reported as Blood clot which may cause swelling, pain, shortness of breath, confusion, or paralysis (under Occasional)

#	Section	Page(s)	Change

5.	ICF – Ph 2	11	Revision of the ICD as Specified Below:
			The condensed risk profile has been modified
			
			• Added New Risk:
			  • Rare: Anemia, kidney problems which may cause tiredness, bruising, swelling, or may require dialysis
			• Increase in Risk Attribution
			  • Changed to Rare from Also Reported on Cediranib Trials But With Insufficient Evidence for Attribution (i.e., added to Risk Profile): Liver damage which may cause yellowing of eyes and skin, swelling; Non-healing surgical site
			
			• Provided Further Clarification:
			  • Blood clot which may cause swelling, pain, shortness of breath (under Occasional) is now reported as Blood clot which may cause swelling, pain, shortness of breath, confusion, or paralysis (under Occasional)

PROTOCOL VERSION DATE: January 03, 2019

NCI PROTOCOL # 8348

DF/HCC PROTOCOL # 09-293

TITLE: Phase I/II study of cediranib and olaparib in combination for treatment of recurrent papillary-serous ovarian, fallopian tube, or peritoneal cancer or for treatment of recurrent triple-negative breast cancer.

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AGENTS:
1. **Cediranib** (NSC 732208; IND124225), supplied by CTEP
2. **Olaparib** (NSC 747856; IND 75918), supplied by CTEP

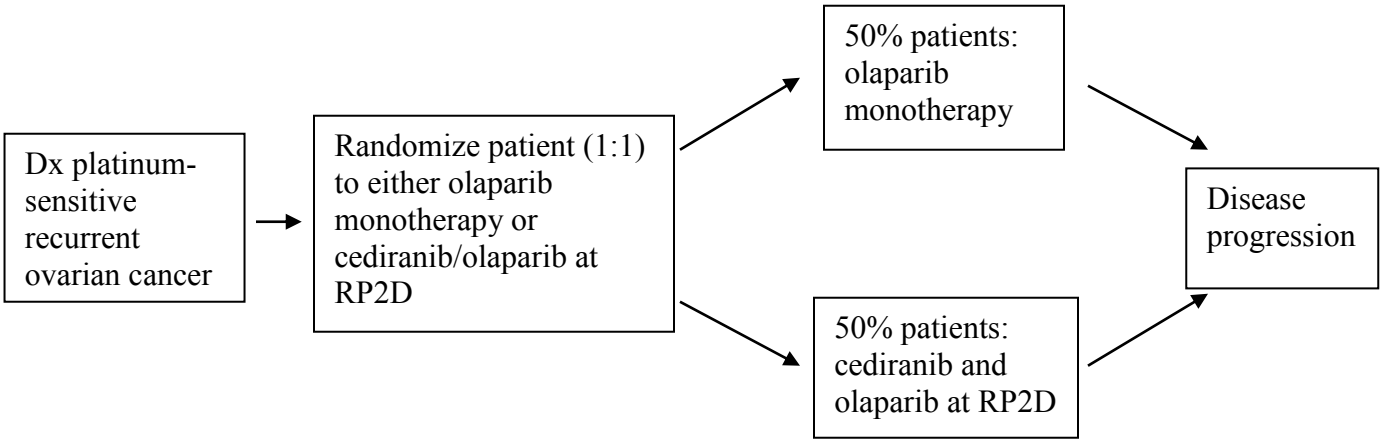
1. SCHEMA

Phase I Dose Escalation Scheme

Dose escalation will proceed within each cohort according to the following scheme:	
Number of Participants with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 participants at the next dose level.
$\geq$ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase II dose. At least 6 participants must be entered at the recommended phase II dose.

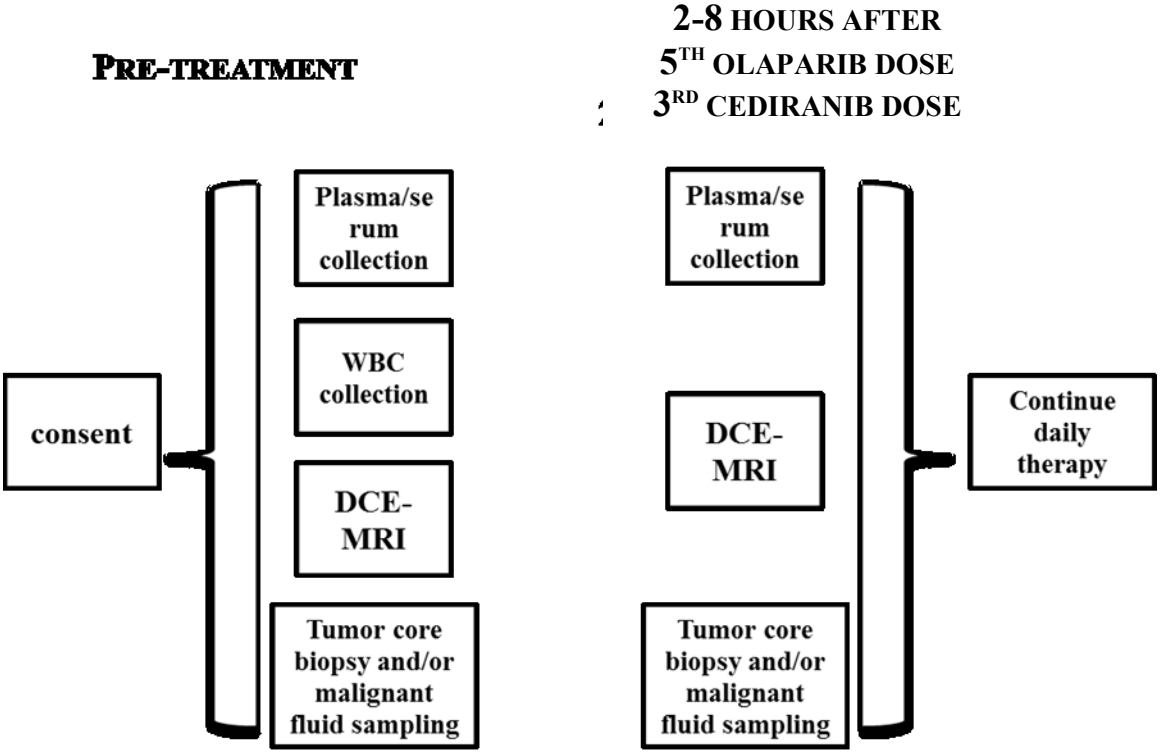
Phase II Component at Recommended Phase 2 Dose (RP2D)

** prior to initiation of treatment, patients will be recruited to the Medical Oncology Branch of the Center for Cancer Research, National Cancer Institute for translational component of study, see schema below.



Translational Sample Acquisition Schema

Schema for sample acquisition for translational objectives for patients at NCI participating in this component**:**



At Progression

Optional tumor core biopsy and/or malignant fluid sampling

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1. OBJECTIVES

1.1. Study Design

This is a Phase I/II trial of the combination of cediranib and olaparib in the treatment of recurrent ovarian, fallopian tube, or peritoneal cancer or in recurrent triple-negative breast cancer to define the safe dose of this combination, followed by a randomized two-arm Phase II study comparing the combination of cediranib and olaparib at the recommended Phase 2 dose (RP2D) as determined in the Phase I portion of the study compared to the control arm of olaparib alone in patients with recurrent platinum-sensitive papillary-serous or endometrioid ovarian, fallopian tube, or peritoneal cancer. A total of up to 148 patients are planned for study enrollment, with up to 28 patients in the phase I dose escalation portion, up to 90 patients in the Phase II randomized portion, and up to 30 patients in the phase I (tablet) dose escalation portion.

1.2. Primary Objectives

1.2.1. Phase 1 Portion: Assess the MTD of cediranib in combination with olaparib in the treatment of recurrent ovarian, fallopian tube, or peritoneal cancer or metastatic triple-negative breast cancer.

1.2.2. Phase 2 Portion: Assess the efficacy (as measured by progression-free survival (PFS)) of the combination of cediranib and olaparib compared to olaparib alone in recurrent grade 2 or 3 platinum-sensitive papillary-serous or endometrioid ovarian, fallopian tube, or peritoneal cancer.

1.2.3. Phase 1-T (olaparib tablet) Portion: Assess the MTD of cediranib in combination with olaparib tablet formulation in the treatment of recurrent ovarian, fallopian tube, or peritoneal cancer.

1.3. Secondary Objectives

1.3.1. Phase 1 Portion: Assess the toxicities of the combination of cediranib and olaparib in the treatment of recurrent ovarian, fallopian tube, or peritoneal cancer or metastatic triple-negative breast cancer. Assess clinical benefit, progression-free survival, and overall survival for patients treated with cediranib and olaparib.

1.3.2. Phase 2 Portion: Assess tumor response, clinical response benefit (response or stable disease as defined by RECIST response criteria x 16 weeks), and overall survival (OS) for patients treated with cediranib and olaparib at the RP2D as compared with patients receiving olaparib alone.

1.3.3. Phase 2 Portion Translational Objectives:

- To evaluate the prognostic and predictive role of measured changes in functional vascular imaging using DCE-MRI between pre-study and day 3.

- To evaluate in an exploratory fashion the predictive or prognostic value of SNPs in key genes involved in angiogenesis and DNA repair.
- To evaluate the predictive value of baseline PBMC PAR incorporation on response to therapy.
- To measure early changes in vascular cytokine production and evaluate in an exploratory fashion that these changes may be predictive or prognostic, or differentially affected by the combination of agents.
- To evaluate early changes to circulating endothelial cells and if these changes are predictive or prognostic.
- To assess changes in measures of DNA damage and repair and angiogenesis in tumor cells (tissue and/or malignant effusions) and correlate to drug/drug/combination.

1.3.4. Phase 1-T (olaparib tablet) Portion: Assess the toxicities of the combination of cediranib and olaparib (tablet formulation) in the treatment of recurrent ovarian, fallopian tube, or peritoneal cancer. Assess clinical benefit, progression-free survival, and overall survival for patients treated with cediranib and olaparib (tablet formulation). Assess the pharmacokinetic profile of cediranib and olaparib (tablet formulation) when administered in combination.

2. BACKGROUND

2.1. Ovarian Cancer

2.1.1. Background

Epithelial ovarian cancer is the most lethal of the gynecologic malignancies, with an estimated 22,000 new cases and 15,000 deaths in the United States in 2008 (Jemal *et al.*, 2008). Patients initially are diagnosed during exploratory laparotomy, during which time surgical staging is performed and gross disease is debulked. Over 70% of patients present with advanced disease, with spread of disease to the upper abdomen (Stage III) or more widely metastatic disease such as malignant pleural effusions or liver/splenic intraparenchymal lesions (Stage IV). Post-operative adjuvant chemotherapy is indicated for all patients with advanced disease, and options include intraperitoneal chemotherapy with cisplatin and paclitaxel or intravenous chemotherapy with carboplatin and paclitaxel. In over 70% of cases, platinum and taxane-based combination therapy results in a clinical complete remission, typically defined as having no evidence of residual tumor, based on a normal serum CA-125 level, normal exam, and normal radiographic study such as a CT scan.

Unfortunately, despite achieving a complete remission, the majority of patients relapse and eventually die of disease, due to the persistence of chemoresistant cancer cells. Despite aggressive surgical and chemotherapeutic approaches, the chance of achieving long-term disease-free survival for subjects with stage III and stage IV disease is only approximately 25% and <10%, respectively (McGuire *et al.*, 1996). Other less common Mullerian tumors such as

primary peritoneal serous cancers and fallopian tube cancers have similar clinical courses and behavior. Thus, it is useful to group these three types of gynecologic cancers into one entity for the purpose of treatment and clinical investigation.

Relapse in these three types of gynecologic cancers is generally incurable, and the goal of treatment changes to one of palliation. The treatment of recurrent ovarian cancer with conventional cytotoxic agents is limited by the development of chemoresistance as well as intolerable side effects. The combination of anti-angiogenic and PARP-inhibitor agents may prove synergistic and perhaps improve overall patient outcomes.

2.1.2. Use of Anti-angiogenic Drugs in Ovarian Cancer

The treatment of ovarian cancer with conventional cytotoxic agents is limited by the development of chemoresistance as well as intolerable side effects. Novel agents that target the angiogenic pathway may improve clinical outcome. Two groups have demonstrated that single agent bevacizumab in recurrent ovarian cancer has a response rate of approximately 18% (Burger *et al.*, 2007; Cannistra *et al.*, 2007). Toxicities of single agent bevacizumab include hypertension, vascular events such as a DVT, pulmonary embolus or stroke, gastrointestinal perforation, and hoarseness. In one study, there was an up to 11% chance of a gastrointestinal perforation, which resulted in early study closure (Cannistra *et al.*, 2007). Additionally, the GOG is currently performing an upfront randomized trial of carboplatin and paclitaxel given intravenously with or without bevacizumab during initial chemotherapy with a second randomization in the maintenance phase to either placebo or continued bevacizumab (GOG 218).

Two studies have been conducted in the United States and Canada of single agent cediranib in women with recurrent ovarian, peritoneal, or fallopian tube cancer. A CTEP-sponsored study within the Dana-Farber/Harvard Cancer Center has included 41 patients to date, and demonstrated an overall 31% clinical benefit response rate, with 19% of patients experiencing a PR and 12.5% with stable disease that lasted at least 16 weeks (Matulonis *et al.*, 2008). Toxicities observed in this study included hypertension, hypothyroidism, diarrhea, abdominal pain, fatigue, and nausea and vomiting. No gastrointestinal perforations were observed. A separate trial conducted through the California consortium also concluded similar results (Hirte *et al.*, 2008).

2.1.3. Use of PARP-inhibitors in Ovarian Cancer

Studies in ovarian cancer have demonstrated a strong hereditary component. Among the genes most commonly linked with a susceptibility to developing ovarian cancer are the BRCA1 and BRCA2 genes. Germline mutations in BRCA1/2 genes have been detected in studies at rates ranging from 8-18% in ovarian cancer patients. The frequency of these BRCA1/2 mutations is markedly increased in Jewish populations.

In addition to germline BRCA1/2 mutations, there are many other mechanism that can affect BRCA1/2 function and thus affect homologous recombination. Deleterious somatic mutations have been observed in both BRCA1 and BRCA2 in approximately 5% of ovarian cancers. Additionally, epigenetic mechanisms such as promoter hyper-methylation can result in aberrant

expression of BRCA1/2 and have been noted in 11-35% of ovarian cancer patients (Yang *et al*., 2006; Press *et al*., 2008). Other proteins involved in the homologous recombination pathway, including Fanconi anemia proteins, ATM, MRE-11, and EMSY, are also affected in a significant proportion of ovarian cancer patients, with an estimate between 17% and 60% (Taniguchi *et al*., 2003; Hughes-Davies *et al*., 2003).

A Phase I study with olaparib included an expansion phase in BRCA-deficient ovarian cancer at 200mg BID (Fong *et al*., 2008). 32 patients with BRCA-deficient ovarian cancer were evaluable for response. 14 of the 32 patients achieved a partial response, while stable disease was seen in an additional 8 patients. An international multicenter Phase II 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 400mg BID (Cohort 1) or 100mg BID (Cohort 2) (Audeh *et al.*, 2010). Responses were observed in 33% (11 of 33) patients enrolled in the 400mg BID cohort and 13% (3 of 24) patients enrolled in the 100mg BID cohort. Preliminary data have also demonstrated activity of olaparib in sporadic ovarian cancers. A Phase II study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer included a cohort of 46 ovarian cancer patients who were known not to carry a germline BRCA mutation, in which an overall response rate of 23.9% was observed (Gelmon *et al*., 2010). Additional studies of olaparib as monotherapy or in combination with a platinum reagent for treatment of metastatic BRCA-deficient ovarian cancer are ongoing. Preliminary results from a Phase II trial investigating olaparib as maintenance therapy following platinum-based therapy for platinum-sensitive serous ovarian cancer demonstrated a significant progression-free survival benefit (8.4 vs. 4.8 months, $p<0.00001$), with subgroup analyses demonstrating evidence of benefit regardless of BRCA status (Ledermann *et al*., 2011). A Phase I study of a different PARP inhibitor MK-4827, has also demonstrated preliminary evidence of single-agent activity in patients with ovarian cancer (Sandhu *et al.*, 2010).

2.2. Study Agents

2.2.1. Cediranib

Mechanism of Action

Cediranib (NSC 732208) is an orally available small molecule that is a multitargeted kinase inhibitor of the VEGFR family and has significant activity against c-kit and PDGFR-beta signaling. VEGF, the ligand to the VEGFR family of tyrosine receptor kinases, has been implicated in tumor blood vessel formation and in disease progression in a wide range of solid tumor malignancies. Expression of this factor is increased by diverse stimuli which include proto-oncogene activation and hypoxia, with the hypoxic state frequently occurring in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature and thereby potentially contributes to tumor progression, as a leaky tumor endothelium can enhance nutrient and catabolite exchange and represent less of a barrier to tumor cell migration during metastasis. Numerous antiangiogenic agents have been developed with the goal of suppressing neovascularization and inhibiting tumor growth and metastasis. Unlike many of these intravenously-administered

antiangiogenic agents, cediranib is a member of an emerging class of novel orally-administered VEGF tyrosine kinase inhibitors (Hennequin *et al.*, 1999; Wedge *et al.,* 2000, 2002).

Two high-affinity receptors for VEGF with associated tyrosine kinase activity have been identified on human vascular endothelium, KDR (kinase insert domain-containing receptor, also known as VEGFR2) and Flt-1 (fms-like tyrosine kinase 1, also known as VEGFR1). Although the relative contributions of KDR and Flt-1 signaling in mediating tumor progression have not been elucidated, a number of studies suggest that KDR has a more predominant role. Cediranib is a potent inhibitor of both KDR (IC_{50}<0.002 μM) and Flt-1 (IC_{50}=0.005 μM) and shows activity against c-kit, platelet-derived growth factor receptor beta (PDGFRβ), and Flt-4 at nanomolar concentrations. It has been shown that cediranib potently and selectively inhibits VEGF-stimulated human umbilical cord vascular endothelial cell (HUVEC) proliferation with an IC_{50} of 4 nM (Ogilvie *et al.*, 2004). Cediranib was also found to have a profound inhibitor effect on vessel area, length, and branching at subnanomolar concentrations using a modified fibroblast/endothelial cell co-culture system. Cediranib's effects on hemodynamic parameters have been studied in an athymic rat xenograft model of human colorectal carcinoma (SW620) using perfusion-permeability dynamic contrast-enhanced magnetic resonance imaging, which demonstrated that in this model, cediranib significantly reduced vascular permeability by 80% ($p<0.005$) and vascular volume by 68% ($p<0.05$) (Bradley *et al.*, 2004).

Non-clinical Efficacy

The effect of cediranib has been 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 orally (PO) at doses from 0.75 to 6 mg/kg/day (2.25-18 mg/m^2/day) in a constant volume of 0.1 mL/10g body weight for 24 to 28 days. Cediranib produced a statistically significant inhibition of tumor growth the xenograft models when dosed at 1.5 mg/kg/day (4.g mg/m^2/day) or higher. In the murine renal cell carcinoma (RENCA) model, cediranib (at a dose of 6.3 mg/kg/day PO) reduced primary tumor growth, metastasis, and microvessel density more potently than any other previously-studied VEGF RTK inhibitor reported in the literature (Drevs *et al.*, 2004). The temporal effects of cediranib administration have been investigated in a transgenic mouse model in which multiple mammary tumors spontaneously develop after two pregnancies (Klinowska *et al.*, 2004). When dosed with cediranib (0.75 to 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 prior to cediranib administration (at doses of 3 and 6 mg/kg/day), dose-dependent growth inhibition occurred as well as tumor regression.

Non-clinical Pharmacology and Toxicology

Non-clinical pharmacology and toxicology company-sponsored cediranib studies have been conducted in rats, dogs, and cynomolgus monkeys. In rats and dogs, oral bioavailability is high, but absorption is relatively slow, with peak plasma concentration (C_{max}) of the agent seen 4-6 hours after PO dosing. Plasma concentrations and exposure are generally linear over the dose range studied in rats. Fecal excretion was the predominant route of elimination (>70% of the dose) in rat, dog, and cynomolgus monkeys after both oral and intravenous administration.

Elimination was rapid in rats and monkeys with over 7% of the dose being recovered in the first 48 hours; in dogs excretion was slightly slower but substantially complete by 7 days.

In vitro data suggest that cediranib at a range of concentrations up to 101 μg/mL demonstrated no inhibition of CYP isozymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1. There were very mild effects seen for CYP2D6, CYP3A4 testosterone and CYP3A4 midazolam, with IC_{50} values estimated to be 32.9, 16.2, and 21.4 μg/mL, respectively. These concentrations are greater than those currently observed in clinical studies, and therefore cediranib is not expected to cause clinically significant drug interactions through inhibition of P450-mediated metabolism of co-administered agents.

VEGF is an important angiogenic factor, a potent physiological mediator of vascular tone, and a potent modulator of capillary permeability, and therefore VEGF receptor inhibition was considered to be the cause of many of the observed pathophysiologic changes. Vascular (myocarditis, choroid plexus) and renal (glomerulosclerosis and tubular degeneration) pathology have been seen in rats, dogs, and primates dosed with cediranib and are considered to be consistent with lesions induced by hypertension, although a direct effect by cediranib on these tissues cannot be excluded. Cediranib has also resulted in pathological findings 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 primates, changes were seen in the gallbladder (mucosal hypertrophy) and bile duct (hyperplasia/hypertrophy).

Pharmacology and Pharmacokinetics in Humans

The company reports that the pharmacokinetics of cediranib support once-daily oral dosing. Although the absolute bioavailability has not been determined, cediranib appears well-absorbed with apparently linear PK for single and multiple doses ranging from 0.5 to 60mg. After multiple once-daily oral doses, steady-state plasma concentrations are attained after approximately 7 days. There is limited accumulation, and steady-state plasma concentrations are predicted by the single-dose PK, indicating no time-dependent changes in PK. Clearance of cediranib is moderate, approximating 64% of nominal hepatic plasma flow, and appears to be extensively through metabolism. <1% of the administered dose of cediranib is excreted unchanged in the urine.

Cediranib has been administered in combination with a number of chemotherapy regimens. Steady-state plasma concentrations of paclitaxel, carboplatin, oxaliplatin, 5-FU (given as mFOLFOX6), docetaxel, pemetrexed, irinotecan, +SN38, gefitinib, or gemcitabine displayed little or no apparent effect (<1.5-fold change) when given in the presence of cediranib. Steady-state PK parameters of cediranib in combination with the chemotherapy agents are comparable to those seen previously with cediranib monotherapy. Additionally, comparison of studies suggests that Western and Japanese patients have similar PK.

Data obtained following a single 45-mg cediranib dose in the presence and absence of a standard high-fat meal showed that food decreases the C_{max} by 33% and AUC by 24%. Cediranib should therefore be administered at least 1 hour before or 2 hours after food.

Safety and Tolerability in Humans

Early clinical data demonstrated that the most common adverse events (AEs) with cediranib included fatigue, diarrhea, nausea, vomiting, hoarseness, hand-foot syndrome, and hypertension.

Hypertension is an expected AE with agents that inhibit VEGF signaling, and is the major cardiovascular AE associated with cediranib treatment. CTC grade 4 hypertension and end-organ damage related to hypertension, such as cerebrovascular events, have been observed with cediranib. Therefore, clinical trials include rigorous monitoring of BP and renal function (creatinine, creatinine clearance, and urinary protein). A hypertension management protocol is incorporated into all clinical study protocols. Patients with pre-existing hypertension may be at particularly high risk of developing moderate or severe hypertension on cediranib and may benefit from having their BP management optimized prior to starting the drug.

Left ventricular dysfunction, in some cases leading to cardiac failure, has been observed in patients with risk factors for left ventricular dysfunction (including previous or concomitant anthracycline treatment). Additional toxicities include bleeding and hemorrhagic episodes such as CNS bleeding that may also be a result of HTN. Some hemorrhagic events 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. Fatigue, hoarseness, diarrhea, hand-foot syndrome, nausea, and vomiting are commonly occurring adverse events in cediranib studies. Dehydration has been observed in clinical studies as a consequence of cediranib- or chemotherapy-related diarrhea or vomiting; chemotherapy-associated anorexia or reduced oral intake may also be the cause. Muscle weakness, proteinuria, dry mouth, and oral mucosal inflammation have been observed in cediranib studies. Increases in transaminases, which are sometimes associated with increases in total bilirubin, have also been seen. Thrombocytopenia, predominantly of CTC grade 1 or 2, has also been observed with cediranib monotherapy or in combination treatment. Reversible posterior leukoencephalopathy syndrome has been observed rarely in patients receiving cediranib. Additionally, cediranib has been associated with increases in TSH; in a small number of patients, clinical hypothyroidism has been reported and may require oral thyroid replacement.

Clinical Studies with Cediranib as Monotherapy

Cediranib has been evaluated as monotherapy in patients with solid tumors and metastatic liver disease (Study D8480C00001), in relapsed or refractory AML (D8480C00002), and in advanced prostate adenocarcinoma (Study D8480C0003). A detailed description of the preliminary data from these studies is provided in Section 5 of the investigator's brochure (IB).

The MTD of cediranib, as determined in Phase I studies detailed in the IB, was 45 mg. However, due to the toxicities observed cediranib 45 mg/day, 30 mg is now considered the starting single agent dose. A number of Phase 2 clinical trials of single agent cediranib have

been conducted in multiple tumor types, with many run through the National Cancer Institute's CTEP program.

Two single-agent studies of cediranib have been conducted in ovarian cancer specifically. The first is a CTEP-sponsored study conducted within the Dana-Farber/Harvard Cancer Center which has included 41 patients to date (Matulonis *et al.*, 2008). The study assessed cediranib monotherapy in women with recurrent ovarian, peritoneal or fallopian tube cancers. Eligibility included prior platinum-based chemotherapy, up to 2 prior lines of chemotherapy in the recurrent setting, ECOG PS of 0 or 1, controlled BP, and normal organ function. Patients could have either platinum-resistant or platinum-sensitive recurrence. 42 patients were enrolled by September 2008, and the study closed in November 2008. The primary endpoint of the study was response rate measured either by RECIST or modified GCIG CA125 criteria, and secondary endpoints included toxicity and progression-free survival. Response was measured after every 2 28-day cycles. After the first 11 patients were enrolled at the original dose of 45 mg/day PO, the protocol was amended to decrease the dose of cediranib to 30mg daily due to toxicities. 36 patients received drug (1 patient never received drug), toxicity assessment was available on 33 patients, and tumor response assessment was made in 32 patients (intention-to-treat population). There was an overall 31% clinical benefit response rate observed; 19% of patients had a PR and 12.5% had stable disease that lasted at least 16 weeks. Toxicities observed included hypertension, hypothyroidism, diarrhea, abdominal pain, fatigue, and nausea and vomiting. A separate trial conducted through the California consortium demonstrated similar results (Hirte *et al.*, 2008).

Cediranib in Combination Therapy

Cediranib was given in combination with one of five different standard chemotherapy regimens in a phase I trial in patients with advanced solid tumors. A total of 46 patients had RECIST assessments performed both at screening/baseline and after Cycle 1 of study treatment, and the data suggested that there was preliminary evidence of some anti-tumor activity with all of the treatment combinations in this study (Shields *et al.*, 2007). Further details are available in Section 5 of the IB.

There are ongoing studies of cediranib in combination with FOLFOX in metastatic colorectal cancer, and a phase 1 study has been conducted of cediranib in combination with carboplatin and paclitaxel in NSCLC (Laurie *et al.*, 2008). In ovarian cancer, ICON6 is a study being run in Europe under the guidance of Dr. Stan Kaye. This is a double-blinded, placebo-controlled multicenter study of the safety and efficacy of concurrent cediranib with platinum-based chemotherapy and single-agent maintenance cediranib in patients with platinum-sensitive recurrent ovarian cancer. Eligible patients include those with recurrent ovarian cancer whose cancer has relapsed more than 6 months following completion of first-line platinum-based treatment, and approximately 2000 patients will be enrolled. Patients will be randomized to one of the three arms: (A) 6 cycles of standard carboplatin and docetaxel given every 3 weeks plus placebo during chemotherapy with placebo for up to 18 months from randomization as maintenance; (B) 6 cycles of carboplatin and docetaxel given every 3 weeks plus cediranib during chemotherapy followed by placebo in maintenance; (C) use of cediranib during both platinum-based chemotherapy as well as up to 18 months of maintenance.

2.2.2. Olaparib

Mechanism of Action

Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerization (PARP) is a unique post-translational modification of histones and other nuclear proteins that contributes to the survival of cells following DNA damage. PARP-1 is one of the enzymes that catalyzes this process, and has been shown to be immediately stimulated by DNA strand breaks. PARP-1 activation leads to DNA repair through the base excision repair (BER) pathway, and cells deficient in PARP-1 have been shown to have delayed DNA repair. Loss of PARP-1 activity in cells or in knockout mice leads to both radio- and chemo-sensitization. PARP-inhibitors can enhance the anti-tumor effects of radiation and DNA-damaging cytotoxic agents (Virag *et al*., 2002; Nguewa *et al.*, 2005).

Olaparib is an orally-bioavailable inhibitor of PARP-1 and has demonstrated monotherapy activity in tumor cells with defects in the homologous recombination pathway, including cells with BRCA1-/- and BRCA2-/- genotype (Bryant *et al.*, 2005; Farmer *et al.*, 2005). Recent studies have indicated that PARP inhibition in BRCA1 and BRCA2 homozygous null cells, but not the isogenic BRCA heterozygous cells, leads to selective cell death.

Non-clinical Pharmacology and Toxicology

Olaparib has demonstrated cellular activity in the low nM range with a cellular dose for 50% inhibition (IC_{50}) of 2nM in HeLa cells. 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.

Olaparib has been tested in dogs and rats. 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. 26-week repeat-dose studies in rats demonstrated doses to be 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 Experience

The first clinical study in man of olaparib (KU-36-92) was a dose-escalation study in patients with advanced solid tumors. Preliminary data demonstrated that olaparib is generally well-tolerated at doses up to and including the MTD of 400mg BID in patients with various solid tumors. As of December 5, 2008, >540 patients with ovarian, breast, pancreatic, melanoma, and other advanced solid tumors have received olaparib, either as monotherapy or in combination with other chemotherapy agents. AEs considered to be associated with olaparib included anemia (mild to moderate), neutropenia (mild to moderate), and thrombocytopenia (generally mild to moderate, sometimes severe), nausea and vomiting (mild to moderate), and fatigue (mild to moderate).

Olaparib has also been studied in an expansion phase in BRCA-deficient ovarian cancer at a dose of 200mg BID. 32 patients with BDOC, the majority of whom were platinum-resistant/refractory were evaluable for response. 14 of 32 patients achieved partial response, 13 meeting GCIG-CA125 criteria, and 10 meeting RECIST criteria. Stable disease was seen in an additional 8 patients (Fong *et al.*, 2008). A multicenter Phase II 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 400mg BID (Cohort 1) or 100mg BID (Cohort 2) (Audeh *et al.*, 2010). Responses were observed in 33% (11 of 33) patients enrolled in the 400mg BID cohort and 13% (3 of 24) patients enrolled in the 100mg BID cohort. A Phase II study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer included a cohort of 46 ovarian cancer patients who were known not to carry a germline BRCA mutation, in which an overall response rate of 23.9% was observed (Gelmon *et al*., 2010). Preliminary results from a Phase II trial investigating olaparib as maintenance therapy following platinum-based therapy for platinum-sensitive serous ovarian cancer demonstrated a significant progression-free survival benefit (8.4 vs. 4.8 months, $p<0.00001$), with subgroup analyses demonstrating evidence of benefit regardless of BRCA status (Ledermann *et al*., 2011). Lee and Kohn and colleagues have examined olaparib with carboplatin in 2 schedules in BRCA1/2 mutation carriers with breast and/or ovarian cancer and women with high grade serous ovarian cancers. They also see activity with over 80% of ovarian cancer patients attaining either disease stabilization or partial response, lasting up to 18+ months (Lee *et al*, 2011). Additional phase I and II trials in both BRCA-deficient and BRCA-competent ovarian cancer are currently ongoing.

2.3. Background for Correlative Studies

2.3.1. Functional Imaging

Functional tumor imaging with dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is capable of evaluating changes in vascularity and quality of index lesions. This imaging modality takes advantage of the fact that angiogenic vessels are hyperpermeable to many macromolecules by assessing the kinetics of contrast inflow and egress from a tumor region of interest. Quantitative parameters such as the volume of transfer constant of contrast agent (K_{trans}) or the blood plasma volume fracti$_{on\ (Vp}$) as well as semi-quantitative measures, such as area under

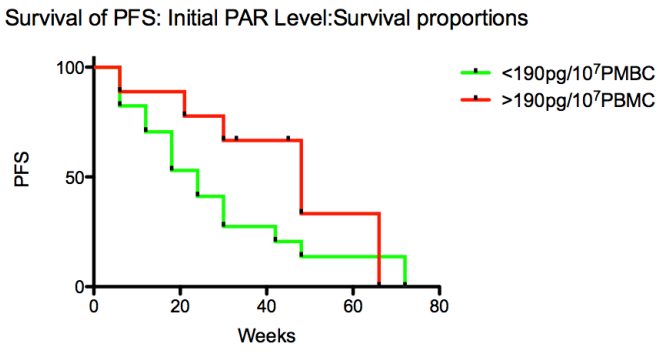
the contrast concentration versus time curve for 90 seconds after contrast injection ($IAUC_{90}$) can be derived from DCE-MRI studies. This modality may provide early indications of treatment effect even before changes in size can be perceived on CT. The molecular imaging studies will be performed for research purposes and will not be used to assess clinical responses as defined by RECIST criteria.

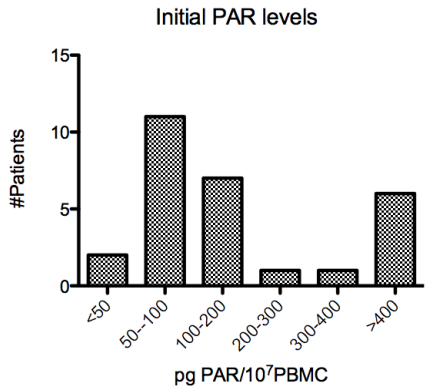
2.3.2. Cytokine Modulation

Most of the inhibitors of angiogenesis, direct and indirect, are associated with altered regulation of proangiogenic and proinflammatory cytokines. These pharmcodynamic changes are consistent across different modalities of angiogenesis inhibition and include induction of circulating VEGF, IL6, IL8, angiopoietin2, and others. To date, these endpoints have not been validated as predictive or prognostic for ovarian cancer response to angiogenesis inhibitors. Economopoulou and colleagues demonstrated that functional γH2AX is required for cell response to aggravated hypoxia indicating a need for DNA repair in angiogenesis NAT MED. Thus, it is posited that there will be greater differences in the pharmacodynamic cytokine response to the combination of cediranib and olaparib.

2.3.3. PAR Incorporation

Incorporation of polyADP ribose moieties at sites of double stranded DNA breaks is a signal to the repair machinery to initiate repair. It is not a marker of repair, per se. It was initially hypothesized that modulation of PAR incorporation by PARP inhibitors would be both proof of mechanism and could be used to predict outcome. Proof of mechanism was shown in an early phase 0 study of ABT-888 (veliparib) by Kummar et al (Kummar *et al.*, 2009) but predictive or prognostic value has not been reported. Preliminary analysis of PBMC PAR incorporation data from the NCI phase 1 study of olaparib and carboplatin suggests that initial PAR incorporation results may be predictive of response to the combination. Those preliminary data using pretherapy results are provocative and form the basis for examining PBMC PAR concentrations as an exploratory endpoint in this study.





Lee, Hays, and Kohn and colleagues evaluated the potential of incorporation of PAR at baseline into PBMC in $BRCA1/2^{mut}$ women accrued to a study of olaparib and carboplatin. ROC analysis of initial PAR levels in each patient measured against her response (PR/CR vs. PD) indicated a

cutoff of 190.5pg PAR/1x10^7 PBMC would yield a sensitivity of 50% and specificity of 100%. This cutoff value was then applied to the evaluable patient cohort (N=29) for stratification prior to comparison with PFS and Wilcoxon analysis. A trend toward increased PFS was observed for patients with initial levels of PAR incorporation in PBMCs less than the ROC-predetermined cutoff (p=0.08; HR 2.05).

2.4. **Rationale**

The treatment of recurrent ovarian cancer with conventional cytotoxic agents is unsatisfactory. Combinations of novel agents with demonstrated effects in ovarian cancer may improve clinical outcome. Results from studies of cediranib and other anti-angiogenic agents have demonstrated single-agent activity in ovarian cancer. Olaparib has demonstrated single-agent activity in BRCA-deficient ovarian cancer and other cells deficient in homologous recombination. Studies have shown that BRCA wild-type ovarian cancers still demonstrate deficiencies in homologous recombination, and studies of olaparib as monotherapy in BRCA wild-type ovarian cancers are ongoing.

2.4.1. Rationale for Selected Approach and Trial Design

- Treatment of recurrent ovarian cancer with conventional cytotoxic agents is limited by development of chemoresistance and intolerable side effects. New therapeutic approaches are needed to improve clinical outcomes.
- Studies of cediranib and other anti-angiogenic agents have demonstrated single-agent activity in ovarian cancer.
- Olaparib is a PARP-1 inhibitor that is active against BRCA-deficient ovarian cancer. It is also active against cells deficient in homologous recombination (HR) in the in vitro setting.
- BRCA wild-type ovarian cancers still demonstrate deficiencies in the homologous recombination pathways. PARP-1 inhibitors have also demonstrated activity in BRCA wild-type ovarian cancers, potentially due to other mechanisms conveying HR-deficiency.
- BRCA-deficient and triple-negative breast cancers share a similar molecular profile in tissue microarrays (Sorlie et al., 2003, Lakhani et al., 2002).
- PARP-inhibition has demonstrated anti-angiogenic effects in preclinical studies. Incubation of endothelial cells with PJ-34 (a PARP inhibitor) inhibited proliferation of the cells (Pyriochou et al., 2008). GPI 15427 (a potent PARP-1 and PARP-2 inhibitor) inhibits in vivo angiogenesis in a matrigel plug assay. PARP-1 knockout mice also demonstrate decreased in vivo angiogenesis by matrigel plug assay when compared with control mice with wild-type PARP-1 activity (Tentori et al., 2007).
- The combination of cediranib and olaparib has the potential for synergistic effect, given the anti-angiogenic effects of PARP-inhibition, while having minimal overlapping toxicities.

As cediranib and olaparib have not been used in combination with one another before, a Phase I dose escalation study will first be completed to determine the MTD of these two agents in

combination. The MTD would be considered the recommended Phase 2 dose (RP2D). The study would then evaluate the effectiveness of the RP2D of the combination of cediranib and olaparib as compared to that of cediranib alone in platinum-sensitive recurrent papillary-serous ovarian, fallopian tube, and peritoneal cancers. The single agent dose of cediranib has been determined to be 30mg daily, and olaparib has been studied in ovarian cancer at a dose of 400mg twice daily in a capsule formulation. Due to concerns regarding the overlapping toxicity of fatigue or unexpected toxicities in setting of combining these two agents for the first time, the starting dose of cediranib will be 20mg daily and that of olaparib will be 100mg twice daily.

3. Participant SELECTION

3.1. Inclusion Criteria

Potentially eligible patients will be screened by their gynecologic oncologist and/or medical oncologist. Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1. For Phase I Portion: Participants must have histologically or cytologically confirmed epithelial ovarian cancer, primary peritoneal serous cancer, fallopian tube cancer, or triple-negative breast cancer.

For Phase II Portion: Participants must have histologically or cytologically Grade 2 or 3 (high-grade) papillary-serous or endometrioid epithelial ovarian cancer, primary peritoneal serous cancer, or fallopian tube cancer. Participants with epithelial ovarian, primary peritoneal, or fallopian tube cancers of other high-grade histologies who carry a known deleterious BRCA germline mutation by standard clinical testing (Myriad BRACAnalysis) will also be considered eligible.

For Phase I-T Portion: Participants must have histologically or cytologically confirmed epithelial ovarian cancer, primary peritoneal serous cancer, or fallopian tube cancer.

3.1.2. Ovarian cancer, primary peritoneal, and fallopian tube participants in the Phase 1 and Phase 1-T portions of this trial must have either measurable cancer by RECIST 1.1 criteria or an elevated CA125 level at least twice the upper limit of normal on two separate occasions at least 1 day but not more than 3 months apart. At least one of the samples should be within 1 week of starting treatment. Patients with both an elevated CA125 and measurable cancer will be followed by RECIST 1.1 criteria. Patients with only an elevated CA125 level will be followed by modified GCIG criteria, as detailed in Section 10.2.

Participants in the Phase II portion of the trial must have measurable disease by RECIST 1.1 criteria.

Breast cancer participants must have measurable disease by RECIST criteria.

3.1.3. Prior therapy:

For Phase I and Phase I-T Portions:

- Prior chemotherapy for ovarian cancer patients must have included a first-line platinum-based regimen with or without intravenous consolidation chemotherapy.
- Breast cancer patients must have recurred post both an adriamycin- and taxane-containing regimen.
- Prior hormonal-based therapy for ovarian, primary peritoneal serous, fallopian tube cancer, or breast cancer is acceptable.

- Patients may not have had a prior PARP-inhibitor in the recurrent or metastatic setting. Prior treatment with BSI-201 is allowed.
- Patients may not have had a prior anti-angiogenic agent in the recurrent or metastatic setting.

For Phase II Portion:

- Prior chemotherapy must have included a first-line platinum-based regimen with or without intravenous consolidation chemotherapy.
- Prior hormonal-based therapy for ovarian, primary peritoneal serous, or fallopian tube cancer is acceptable.
- Patients may not have previously received a PARP-inhibitor. Prior treatment with BSI-201 is allowed.
- Patients may not have had a prior anti-angiogenic agent in the recurrent setting.
- Patients may have received up to 1 non-platinum-based line of therapy in the recurrent setting.
- Patients may have received an unlimited number of platinum-based therapies in the recurrent setting.
- Patients should have platinum-sensitive disease, where platinum-sensitive disease is defined as having had a > 6 month interval since last receiving platinum therapy prior to disease recurrence. Patients must have had a prior response while on the platinum-containing regimen and cannot have experienced disease progression while receiving platinum.

Subjects may begin cediranib and olaparib at least 3 weeks after their last dose of chemotherapy or hormonal therapy, assuming they are otherwise eligible.

3.1.4. Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of cediranib or olaparib in participants < 18 years of age, children are excluded from this study but will be eligible for future pediatric trials.

3.1.5. Estimated life expectancy of greater than 6 months.

3.1.6. ECOG performance status 0 or 1 (Karnofsky > 60%, see Appendix A).

3.1.7. Participants must have adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- Hemoglobin > 9 g/dL
  - For patients enrolled to the Phase 1-T portion of the protocol, the Hemoglobin should be ≥ 10 g/dL
- Total bilirubin within 1.5 times the upper limit of normal institutional limits
- AST (SGOT)/ALT (SGPT) ≤ 2.5 × institutional upper limit of normal
- Creatinine ≤ the institutional upper limit of normal or creatinine clearance ≥ 60 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal

- Less than or equal to 1+ proteinuria on two consecutive dipsticks taken no less than 1 week apart, or < 1 gm protein on 24-hour urine collection or a urine protein:creatinine ratio of < 1.
- Troponin T or I within normal institutional limits
- Coagulation parameters (INR, aPTT) within 1.25 × upper limit of normal institutional limits, except where a Lupus anti-coagulant has been confirmed

3.1.8. Toxicities of prior therapy (excepting alopecia) should be resolved to less than or equal to Grade 1 as per NCI-CTCAE v4.0 (located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Patients with long-standing stable grade 2 neuropathy may be considered after discussion with the overall PI.

3.1.9. 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. Subjects with prior cancer treated with a curative intent with no evidence of recurrent disease 5 years following diagnosis and judged by the investigator to be at low risk of recurrence are eligible. Subjects with any other concomitant or prior invasive malignancies are ineligible.

3.1.10. Patients who have the following risk factors are considered to be at increased risk for cardiac toxicities. These patients should have increased monitoring (see study calendar Section 9.0)

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- A New York Heart Association classification of II controlled with treatment (see Appendix E)
- 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).

3.1.11. 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, for the duration of study participation, and for 3 months following treatment discontinuation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

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

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

3.1.14. Patients must be willing and able to check and record daily blood pressure readings.

3.2. **Exclusion Criteria**

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1. Participants who have had chemotherapy or radiotherapy within 3 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 3 weeks earlier.

3.2.2. Participants may not be receiving any other investigational agents nor have participated in an investigational trial within the past 4 weeks. Subjects may not have received prior treatment affecting the VEGF pathway in the recurrent setting, including thalidomide, bevacizumab, sunitinib, or sorafenib. In the Phase I portion of the trial, subjects may not have received prior treatment with oregovomab (OvaRex) or any other antibodies that may interfere with CA-125 measurements.

3.2.3. Patients with untreated brain metastases, spinal cord compression, or evidence of symptomatic brain metastases or leptomeningeal disease as noted on CT or MRI scans should not be included on this study, since neurologic dysfunction may confound the evaluation of neurologic and other adverse events. Screening imaging to rule out brain metastases is not required for screening, but should be performed prior to study enrollment if clinically indicated. Patients with treated brain metastases and resolution of any associated symptoms must demonstrate stable post-therapeutic imaging for at least 6 months following therapy prior to starting study drug.

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

3.2.5. Participants receiving any medications or substances that are *strong* inhibitors or inducers of CYP3A4 are ineligible. A list of CYP3A4 inhibitors and inducers is provided in Appendix D. Dihydropyridine calcium-channel blockers are permitted for management of hypertension.

3.2.6. Patients with any of the following:

- History of myocardial infarction within six months
- Patients with QTc prolongation > 500 msec or other significant ECG abnormality noted within 14 days of treatment.
    - For patients enrolled in the Phase 1-T portion of the protocol, the QTc should not exceed 470 msec.
- NYHA classification of III or IV
- If cardiac function assessment is clinically indicated or performed: LVEF less than normal per institutional guidelines, or < 55%, if threshold for normal not otherwise specified by institutional guidelines.
- Condition requiring concurrent use of drugs or biologics with pro-arrhythmic potential (see Appendix F).

3.2.7. History of stroke or transient ischemic attack within six months.

3.2.8. Patients may not have any evidence of pre-existing inadequately controlled hypertension (defined as a systolic BP of >140 mmHg or a diastolic BP of >90 mmHg), and must have a normal blood pressure (≤140/90 mmHg) taken in the clinic setting by a medical professional within 2 weeks prior to starting study. Patients with hypertension may be managed with up to a maximum of three antihypertensive medications. Patients who are on three antihypertensive medications must be actively followed by a cardiologist or blood pressure specialist for management of blood pressure while on protocol.

3.2.9. Any prior history of hypertensive crisis or hypertensive encephalopathy

3.2.10. Clinical significant peripheral vascular disease or vascular disease (aortic aneurysm or aortic dissection)

3.2.11. Unstable angina

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

3.2.13. History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess.

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

3.2.15. Current dependency on IV hydration or TPN.

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

3.2.17. 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.

3.2.18. Pregnant women are excluded from this study because cediranib and olaparib are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with cediranib and olaparib, breastfeeding should be discontinued if the mother is treated with cediranib or olaparib. These potential risks may also apply to other agents used in this study.

3.2.19. Known HIV-positive individuals are ineligible because of the potential for pharmacokinetic interactions with cediranib or olaparib. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.20. Patients may not use natural herbal products or other "folk remedies" while participating in this study.

3.2.21. No features suggestive of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) on peripheral blood smear or bone marrow biopsy, if clinically indicated.

3.3. Inclusion of Women, Minorities and Other Underrepresented Populations

Both genders and members of all races and ethnic groups are eligible for this trial.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	9	+		=	
Not Hispanic or Latino	153	+		=	
Ethnic Category: Total of all subjects	162 (A1)	+	0 (B1)	=	(C1)
Racial Category					
American Indian or Alaskan Native	0	+		=	
Asian	12	+		=	
Black or African American	5	+		=	
Native Hawaiian or other Pacific Islander	0	+		=	
White	145	+		=	
Racial Category: Total of all subjects	162 (A2)	+	0 (B2)	=	(C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

Accrual Rate: 2-3 (Ph 1); 5-6 (Ph 2) 2-3 (Ph 1-T): ____ pts/month

Total Expected Accrual: 127 Min 162 Max

Projected Start Date of Study: _____

4. REGISTRATION PROCEDURES

4.1. General Guidelines for DF/HCC and DF/PCC Institutions

Eligible patients will be entered on study centrally through the Quality Assurance Office for Clinical Trials (QACT) at the Dana-Farber Cancer Institute at the time of study enrollment. Completed QACT eligibility checklists and signed consent forms should be faxed to the QACT at 617-632-2295 prior to subjects starting protocol treatment. The checklist will be reviewed at that time and the subject registered by the QACT Protocol Registrars (617-632-3761).

Following registration, patients should begin protocol treatment within 5 days. Other issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

4.2. Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

Randomization can only be done between normal QACT business hours, 8:00 AM to 5:00 PM Eastern Standard Time.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

4.3. Registration Process for non DF/HCC Institutions

Registration for non-DF/HCC Institutions will be as detailed in the Data Safety Monitoring Plan (DSMP). Please refer to the DSMP, Appendix G, Section 5.7 for specific procedures.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for cediranib and olaparib are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Phase I

Each cycle will be 28 days (4 weeks). For the Phase I component of this study, treatment cohorts will consist of 3 to 6 patients and the dose escalation schedule will be as follows. Participants enrolled to the Phase I portion of the study will continue treatment with olaparib capsule formulation.

	Dose Level	Cediranib	Olaparib (capsule)
	-1	15mg PO daily	100mg PO BID
Starting dose →	0	20mg PO daily	100mg PO BID
	1	20mg PO daily	200mg PO BID
	2	30mg PO daily	200mg PO BID
	3	30mg PO daily	400mg PO BID

Phase I-T

For the Phase I-T component of this study, treatment cohorts will consist of 3 to 6 patients. Two separate cohorts of dose escalation will be accrued, one with a dosing of cediranib at 30mg daily (Phase I-TA) and a second at cediranib dosing of 20mg daily (Phase I-TB). The two Phase I-T

dose escalation schemes will enroll in parallel. Participants enrolled to the Phase I-T portion of the study will receive treatment with the olaparib tablet formulation. The dose escalation schedule for the two cohorts will be per the following tables. If the cohort of patients enrolled in a given dose level completes the DLT assessment window without experiencing a DLT in the first three patients or with 1 or fewer DLTs in six patients, the next higher dose level may be assessed.

Phase 1-TA Dose Escalation: Cediranib 30mg

	Dose Level	Cediranib	Olaparib (tablet)
	-1-TA	30mg PO daily	100mg PO BID
Starting dose →	0-TA	30mg PO daily	150mg PO BID
	1-TA	30mg PO daily	200mg PO BID
	2-TA	30mg PO daily	250mg PO BID
	3-TA	30mg PO daily	300mg PO BID

Phase 1-TB Dose Escalation: Cediranib 20mg

	Dose Level	Cediranib	Olaparib (tablet)
	-1-TB	20mg PO daily	150mg PO BID
Starting dose →	0-TB	20mg PO daily	200mg PO BID
	1-TB	20mg PO daily	250mg PO BID
	2-TB	20mg PO daily	300mg PO BID

Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0). CTCAE v4.0 is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Dose escalation to the next dose level will occur when the preceding cohort reaches the end of Cycle 1. Patients who do not complete both treatments in cycle 1 for reasons other than cediranib or olaparib toxicity will be replaced. Toxicity data for each cohort will be reviewed prior to dose escalation. Intra-patient dose escalation will be allowed at the discretion of the investigator and overall trial PI for patients following their completion of Cycle 2 if the following criteria are met: the patient had no > grade 1 toxicities secondary to study treatment except for grade 2 or 3 HTN or nausea no greater than grade 1 after treatment with concurrent medications, the subsequent dose cohort has completed Cycle 1, and evaluation of DLTs has been completed for the subsequent dose cohort and the dose was deemed to be safe due to ≤ grade 2 toxicities. Dose escalation will occur for both cediranib and olaparib according to the dose escalation schema. Patients can be dose-escalated multiple times as long as they continue to meet criteria and do not exceed the final protocol-specified dose level (dose Level 3). All intra-patient dose escalations must be discussed and approved by the overall trial PI. If treatment-related toxicities related to one of the study drugs restricts further escalation of that drug, a modification to the dose escalation schema may be considered.

Phase I-T PK expansion

Once the MTD has been established during the Phase 1-T, two PK expansion cohorts of 6 evaluable patients each will be enrolled for pharmacokinetic studies. Participants in this expansion will receive a one week of either single-agent cediranib (Cohort 1-T PKced) or single-

agent olaparib (tablet formulation; Cohort 1-T PKolap) prior to starting cycle 1 of combination cediranib and olaparib (tablet formulation). Full details of the PK evaluation schedule are outlined in Section 8.14. Participants must be able to continue on study drug without any dose holds through Cycle 1 Day 16 of treatment to be considered fully evaluable for PK studies.

Participants participating in the PK expansion cohorts will take their study drugs on the following schedule once combination dosing has started:

1. Cediranib tablet(s) in the morning on an empty stomach (at least 2 hours after eating)
2. Light meal ~1 hour after taking cediranib
3. Morning olaparib tablet(s) after light meal
4. Evening olaparib tablet(s) 12 hours after morning olaparib dose, taken after a light meal

Phase II

For the Phase 2 portion of this study, patients will be randomized in 1:1 ratio to one of the two following arms:

1. Olaparib 400mg BID (capsule)
2. Cediranib and olaparib at the RP2D (cediranib 30mg daily and olaparib 200mg BID (capsule)) derived from the Phase I portion of this study

Participants enrolled to the Phase II portion of the study will continue treatment with olaparib capsule formulation.

All patients must meet the eligibility criteria for the Phase II portion of the study, as outlined in Section 3. Patient randomization will be stratified based upon:

1. Prior receipt of anti-angiogenic therapy.
2. BRCA mutation status (carrier, non-carrier, unknown).

5.1. Pre-treatment Criteria

5.1.1. Screening Visit: Patients must meet criteria at screening as outlined in Section 3.1.

5.1.2. Hematologic Parameters for treatment:

Absolute Neutrophil Count:

- Cycle 1, Day 1: $\geq 1500/mm^3$
- Cycles 2 and Beyond, Day 1: $\geq 1000/mm^3$

For Phase 1-T patients:

- Hemoglobin:
  - Cycle 1, Day 1: >=10g/dL
  - Cycles 2 and beyond, Day 1: Per Table in Section 6.3.1
- Platelets:

- Cycle 1, Day 1: >=100,000/mcL
- Cycles 2 and beyond, Day 1: Per Table in Seciton 6.3.1

5.1.3. <u>All Cycles, Day 1</u>: Patients must have all of the following:

- Adequate blood pressure control as detailed in Section 6.3.2.
- Serum creatinine $\leq$ 1.5 × the institutional upper limit of normal
- Liver function test $\leq$ 2.5 × upper limit of normal.
- ECOG performance status of 0 or 1.
- No evidence of life-threatening medical problems.

5.1.4. <u>Pre-Cycle 1 Therapy</u>: Translational Component

- All patients will be *strongly* encouraged to participate in the translational component of the trial. Travel to and from the NCI and all costs of imaging, blood draws, biopsy, or fluid sampling done at the NCI will be provided in kind. A stipend to assist with cost of the local stay during this aspect of the trial will be provided, or the patient can elect hospital admission at no cost.
- Biopsiability will be determined prior to scheduling the NCI visit using most recent tumor imaging. This will be followed by an on-study chest/abdominal/pelvic CT with oral and IV contrast obtained the day of evaluation at NCI. A copy of this scan will be provided to the home institution for use in subsequent tumor measurements.
- Patients will be seen at NCI with a copy of their signed protocol consent from their home institution.
- Drug therapy will be initiated after acquisition of initial translational components and dispensed for the 28-day cycle.
- Translational component sample acquisition will occur:
  - Prior to starting therapy
  - Prior to day 3: 2-8 hours after the 5th dose of olaparib (d1 will start with the am dose) and the 3rd dose of cediranib (the first dose of cediranib will be administered at the same time as the first dose of olaparib).

Process	Pre-treatment	Day 3
Blood for PBMCs, DNA, and CECs	X	X
Plasma and serum for cytokines	X	X
DCE-MRI imaging	X	X
Biopsy: core of tumor, involved skin, or malignant effusion sampling	X	X

5.2. Agent Administration

5.2.1. Cediranib

Cediranib at the appropriate dose level will be given orally continuously each morning on an empty stomach, either 1 hour before or 2 hours after breakfast. Subjects should not "make up" a missed dose or a dose that was vomited. Subjects should take cediranib with a glass of water. Subjects should avoid grapefruit juice while on study, due to P450 interactions. Cediranib may be taken at the same time as the morning olaparib dose.

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

Frequent blood pressure monitoring is important in patients receiving cediranib. Clinical trials of cediranib demonstrate that increases in blood pressure may occur following dosing with cediranib for a number of weeks and that these increases may occur relatively quickly when starting the drug. Patients will be asked to record twice-daily blood pressure readings (Appendix C). If two successive systolic readings are >140 mmHg OR two successive diastolic readings are >90 mmHg OR any combination of elevated systolic and diastolic blood pressure are observed, patients will be instructed to contact their physician as soon as possible. Patients should seek medical advice if their BP exceeds 180 mmHg (systolic) or 105 mmHg (diastolic) at any time and should also be encouraged to contact their physician if they are concerned about any symptoms that may be associated with high blood pressure (*e.g.*, headache). Section 6 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension.

5.2.2. Olaparib

<u>Olaparib Capsules</u> (Phase I and Phase II Participants)

Olaparib at the appropriate dose level will be given orally continuously twice daily on an empty stomach. The correct number of 50mg capsules comprising the appropriate dose should be taken at the same times each day with approximately 240 mL of water. Patients should take olaparib on an empty stomach either 1 hour before or 2 hours after meals. The olaparib capsules should be swallowed whole and not chewed, crushed, dissolved, or divided.

Olaparib will be dispensed at the start of each cycle. Patients will be provided with a pill diary (Appendix B), instructed in its use, and asked to bring it with them to each appointment.

If vomiting occurs shortly after the olaparib capsules are swallowed, the dose should only be replaced if all of the intact capsules 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.

Olaparib Tablets (Phase I-T Participants)

Olaparib at the appropriate dose level will be given orally continuously twice daily on an empty stomach. The correct number of 25mg, 100mg, or 150mg tablets comprising the appropriate dose should be taken at the same times each day with approximately 240 mL of water. Patients should take olaparib on an empty stomach either 1 hour before or 2 hours after meals. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

Olaparib will be dispensed at the start of each cycle. Patients will be provided with a pill diary (Appendix B), instructed in its use, and asked to bring it with them to each appointment.

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.

5.3. Definition of Dose-Limiting Toxicity

Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0). CTCAE v4.0 is identified and located on the CTEP website at (http://ctep.cancer/gov/protocolDevelopment/electronic_applications/ctc.htm). Dose-limiting toxicity (DLT) refers to toxicities experienced during the first cycle of treatment. A DLT is defined as any of the following:

- **Non-Hematologic Toxicity**
  - Grade 3 or 4 events, excluding
    - Grade 3 fatigue
    - Grade 3 hypertension controlled with anti-hypertensive therapy.
    - Grade 3 hypophosphatemia
    - Grade 3 hyponatremia
- **Hematologic Toxicity**
  - Grade 4 neutropenia of ≥ 4 days duration
  - Grade 4 neutropenia of any duration with fever or documented infection
  - All other hematologic toxicities of Grade 4
  - Inability to take 75% or more of the planned dose in Cycle 1 due to treatment-related AEs

Management and dose modifications associated with the above adverse events are outlined in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications).

Dose escalation will proceed within each cohort according to the following scheme.

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase II dose. At least 6 participants must be entered at the recommended phase II dose.

If one patient develops a DLT, then the cohort will be expanded to include a total of 6 patients. If greater than or equal to two patients develop DLT, then that dose level will be considered the maximum administered dose (MAD), and further dose escalation will be terminated. A total of 6 patients will be treated at the next lower dose. The maximum tolerated dose (MTD) will be the dose at which no more than 1 patient develops DLT when at least 6 patients have been treated.

5.4. General Concomitant Medication and Supportive Care Guidelines

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

Cediranib demonstrated minimal inhibitor effects on the activity of CYP3A4 (testosterone and midazolam) in vitro, although the IC50 was far in excess of the clinically relevant

concentrations. Based on in vitro and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. However, in vitro data have also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4. Given this data, potent inhibitors or inducers of CYP3A4 (as outlined in Appendix D) 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. Neupogen and other bone marrow-supportive agents, including erythropoiesis-stimulating agents, are not allowed during treatment.

5.5. Duration of Therapy

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

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

5.6. Duration of Follow Up

Participants will be followed for 3 years after removal from study treatment or until death, whichever occurs first. Participants removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Participants' vital status will be followed every 6 months following removal from the study treatment. Date and cause of death should be provided for participants who become deceased within the 3 year interval following removal from the study treatment.

5.7. Criteria for Removal from Study Treatment

Participants will be removed from study treatment when any of the criteria listed in Section 5.5 applies. The reason for study treatment removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Joyce Liu, MD at 617-632-3352 (pager).

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0). CTCAE v 5.0 is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

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

6.1. Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

6.1.1. CAEPRs for CTEP-Supplied Investigational Agents

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete 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 Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of Aes (the ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (http://ctep.cancer.gov/) for further clarification. The CAEPR may not provide frequency data; if not, refer to the Investigator's Brochure for this information.

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)***

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%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lymphocyte count decreased		
	Neutrophil count decreased		
	Platelet count decreased		
	Thyroid stimulating hormone increased		***Thyroid stimulating hormone increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Generalized muscle weakness		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
	Lethargy		
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	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)***

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%)**	
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.

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 2073 patients.* Below is the CAEPR for Olaparib (AZD2281).

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

Version 2.3, June 18, 2018[1]

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 2073]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
	Creatinine increased		
	Lymphocyte count decreased		
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 2073]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	

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

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

CARDIAC DISORDERS - Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Mucositis oral; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Gastrointestinal anastomotic leak; Injury, poisoning and procedural complications - Other (vena cava injury); Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Hemoglobin increased; Lipase increased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Bone pain; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Myalgia; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (decreased glomerular filtration rate); Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Pruritus; Rash maculo-papular
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Thromboembolic event

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

6.1.2. Adverse Event Lists for olaparib

Adverse events observed with olaparib are detailed in the Investigator's Brochure (IB). As of October 2, 2013, >2100 patients have received olaparib in doses ranging from 10mg daily to 600mg BID, either as monotherapy or in combination with other chemotherapy agents (liposomal doxorubicin, cisplatin, dacarbazine, gemcitabine, gemcitabine+cisplatin, carboplatin, carboplatin+paclitaxel, paclitaxel, topotecan, irinotecan, or bevacizumab). Preliminary unvalidated safety data are available for several studies and are detailed in the IB.

Aes considered to be associated with administration of olaparib included laboratory findings and/or clinical diagnoses of anemia (generally mild to moderate, CTC grade 1 or 2), neutropenia (predominantly mild to moderate, CTC grade 1 or 2), thrombocytopenia (generally mild to moderate, CTC grade 1 or 2; sometimes severe, CTC grade 3 or 4), nausea and vomiting (generally mild to moderate, CTC grade 1 or 2, intermittent and manageable on continued treatment), and fatigue (generally intermittent, of mild to moderate intensity CTC grade 1 or 2). Pneumonitis events with no consistent clinical pattern have been reported in a small number of patients. Rare hematologic malignancies, including myelodysplasia, have also been reported. Please see the table below, titled "Summary of Adverse Drug Reactions from Completed Clinical Trials of Olaparib," for a summary of the adverse drug reactions from completed trials of olaparib.

In the first clinical study in man, a total of 98 patients in the study were evaluable for safety. As expected in patients with advanced cancer, all of the patients experienced at least one adverse event. In total, 81 patients (82.7%) experienced at least one adverse event that the investigator attributed to study medication. Most of the Aes were mild to moderate in intensity. The number of patients with CTC grade ≥3 events attributed to study medication was low (24 patients, 21.4%) and increased with increasing dose. The observed Aes in each system are detailed below.

- **Gastrointestinal Disorders**
  The most common gastrointestinal Aes were nausea (56 of 98 patients, 57%) and vomiting (44 of 98 patients, 45%). Most were of mild to moderate intensity (CTC grade 1 or 2), intermittent, and manageable on continued treatment. Abdominal pain (24 of 98 patients, 24.5%), constipation (18 of 98 patients, 18.4%), and diarrhea (25 of 98 patients, 25.5%) were also observed.

- **General Disorders**
  The most common general AE reported was fatigue, which was observed in 52 patients (53%). Cases of fatigue were generally intermittent and of mild to moderate intensity (CTC grade 1 or 2). Other Aes included pyrexia (10 patients, 10%) and peripheral edema (16 patients, 16%).

- **Cardiac Disorders**

29 patients reported mild (CTC grade 1), asymptomatic tachycardia. None of these cases required treatment, and all events were considered to be unrelated to study drug.

- **Nervous System Disorders**
  The most common nervous system Aes reported were headache (15%), dizziness (11%), and dysgeusia (13%). Other reported Aes included somnolence, attention or mental impairment, cognitive disorder, dizziness, depression, and memory impairment.

- **Hematologic Disorders**
  Laboratory findings and/or clinical diagnoses of anemia (generally mild to moderate, CTC grade 1 or 2), neutropenia (predominantly mild to moderate, CTC grade 1 or 2), and thrombocytopenia (generally mild to moderate, CTC grade 1 or 2, sometimes severe) were observed. The incidence of anemia was 26%, neutropenia was 1%, and thrombocytopenia was 5%. A few cases of myelodysplasia have been reported on studies including olaparib. Additionally, data from study D0810C00002 have demonstrated increases in MCV in approximately 30% of patients, especially in those receiving greater than 6 cycles of treatment, mild and moderate in intensity, and asymptomatic in nature. No clinical consequences have been associated with this finding.

MDS/AML have been reported in <1% of patients exposed to olaparib. 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.

New primary malignancies have been reported in a small number of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases.

Pneumonitis events have been reported in <1% of patients receiving olaparib. 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).

6.2. Dose Modifications/Delays

In the phase 1 and phase 1-T components of this study, doses of cediranib and olaparib will be administered at the same dose level throughout a cycle if no DLTs occur. In cycle 1, patients experiencing non-hematologic Grade 2 Aes (or Grade 3 fatigue or hypertension) may have treatment held for up to 7 days for toxicity management. Treatment may then be resumed at the same dose level. Inability to take at least 75% of the planned dose of cediranib and olaparib in Cycle 1 due to drug-related toxicity is considered a DLT. If any individual patient develops a DLT, treatment for this patient will be stopped. If the toxicity is not resolved within 14 days, the patient will be removed from the study. Patients who experienced a DLT whose toxicity has

resolved to baseline or Grade 1 and whose therapy has been discontinued for less than 14 days may resume therapy at the previous (next lower) dose level if necessary. For patients who experience a DLT in the first cycle of the first cohort (cediranib 20mg daily and olaparib 100mg BID) whose toxicity has resolved to baseline or Grade 1 and whose therapy has been discontinued for less than 14 days, the dose may be reduced to cediranib 15mg daily and olaparib 100mg BID. During the DLT assessment period, both drugs must be held if there is an indication for either drug to be held.

For patients experiencing non-hematologic Grade 2 Aes (or Grade 3 fatigue or hypertension) in cycles 2 or greater, treatment may be held for up to 14 days for toxicity management if necessary. The treating physician may decide to hold treatment to ensure patient safety when grading and/or attribution is unclear. Patients whose treatment has been held for ≤7 days may then resume treatment at the same dose level. If treatment is held for >7 days, please see Section 6.3.1 regarding dose modifications. For patients in the phase 1 and 1-T portions of the study in cycles 2 and beyond, dose modifications/delays should be managed as per Section 6.3.1. Tables for cediranib and olaparib dosing levels are provided in Sections 6.2.1 and 6.2.2.

In the phase 2 component of this study, dose modifications, and general management of Aes will be outlined as in Section 6.3.1. Dose modifications and delays for specific toxicities of hypertension, proteinuria, decrease in LVEF, diarrhea, fever and neutropenia, thyroid toxicities, and RPLS will be as further outlined in specific subsections in Section 6.3.

6.2.1. Table for Cediranib Dose Modification*

Dose Level	Cediranib
-2	15mg daily
-1	20mg daily
1	30mg daily

* Presuming patients are being dosed at the maximum Phase 1 dose level of cediranib 30mg daily or being dosed as the starting phase 2 dose level of cediranib 30mg daily. Patients who are being treated at a different dose level on the Phase 1 or Phase 1-T portions of this trial may be dose-reduced per this table but may not be dose-escalated except as detailed in Section 5.

6.2.2. Tables for Olaparib Dose Modification

Phase I:

Dose Level	Olaparib (capsule)
-2	100mg twice daily
-1	200mg twice daily
1*	400mg twice daily

* This dose level is applicable only for patients who were dosed at the maximum Phase 1 dose level of olaparib 400mg twice daily. Patients who are being treated at a different dose level on the Phase 1 portion of this trial may be dose-reduced per this table but may not be dose-escalated except as detailed in Section 5.

Phase I-TA:

Dose Level	Olaparib (tablet)
-2	100mg twice daily
-1	150mg twice daily
1	200mg twice daily
2	250mg twice daily
3	300mg twice daily

* Patients may be dose-reduced per this table but may not be dose-escalated except as detailed in Section 5.

Phase I-TB:

Dose Level	Olaparib (tablet)
-3	150mg twice daily
-2	200mg twice daily
-1	250mg twice daily
1	300mg twice daily

* Patients may be dose-reduced per this table but may not be dose-escalated except as detailed in Section 5.

Phase II:

For patients receiving olaparib **monotherapy**:

Dose Level	Olaparib (capsule)
-2	100mg twice daily
-1	200mg twice daily
1	400mg twice daily

For patients receiving olaparib and cediranib **combination therapy**:

Dose Level	Olaparib (capsule)
-2	100mg twice daily
-1	150mg twice daily
1	200mg twice daily

6.3. Toxicity Management

The management of general adverse events not otherwise specified will be as per the table in Section 6.3.1. Management of specific toxicities, including hypertension, proteinuria, decreased in LVEF, diarrhea, fever and neutropenia, thyroid toxicities, and RPLS will be as further outlined in specific subsections in Section 6.3.

6.3.1. Dose Modifications and Management of Cediranib and Olaparib Toxicities

General Management of Adverse Events (Non-Hematologic)	
Observation	**Action**
AE resolves promptly with supportive care	Maintain dose level
Any grade 2 non-hematologic AE or grade 3 fatigue related to cediranib or olaparib that persists despite maximal support.	Hold study drug(s)[1] for up to 14 days until toxicity resolves to ≤ grade 1.[3] Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Sections 6.2.1 and 6.2.2, at the treating investigator's discretion. 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.
Any ≥ grade 3 non-hematologic (excluding grade 3 fatigue or 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.[3] Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Sections 6.2.1 and 6.2.2, at the treating investigator's discretion. The overall 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.[2] 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 For patients receiving both cediranib and olaparib after the DLT assessment period has completed in the Phase 1 or Phase 1-T or for patients enrolled to the cediranib/olaparib arm in the Phase 2 -- if the observed AE is specifically attributed to only one of the drugs, that drug may be held while the patient continues to receive the drug not associated with the observed AE. The time a given drug is held should not exceed 14 days.
2 Excluding hypertension, see below 6.3.2
3 For thromboembolic events, treatment may be resumed at the discretion of the investigator once patient is asymptomatic. For weight loss events, treatment may be resumed at the discretion of the investigator once weight has stabilized.

Dose Modification and Management of Hematologic Adverse Events	
Observation	**Action**
Absolute neutrophil count ≥ 1000/mcL **AND** Platelets ≥ 75,000/mcL **AND** Hemoglobin ≥ 8 mg/dL	Maintain dose level
Absolute neutrophil count < 1000/mcL **OR** Platelets < 75,000/mcL **OR** Hemoglobin < 8 mg/dL	Hold treatment for up to 14 days until absolute neutrophil count ≥ 1000/mcL, platelets ≥ 75,000/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 Sections 6.2.1 and 6.2.2, at the treating investigator's discretion. The overall PI of the study should be informed regarding all dose modifications. Patients whose counts have not recovered to absolute neutrophil count ≥ 1000/mcL, platelets ≥ 75,000/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 ≥ 75,000/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 in the dual therapy arm, 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.

6.3.2. Hypertension Management

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 (see Appendix C). See Table 1 for hypertension management.

Of note, hypertension onset can be acute and significant when cediranib treatment is initiated. For this reason, patients must have their blood pressure diaries reviewed by the study team weekly during the first 8 weeks of treatment.

Table 1: Hypertension Monitoring and Management

- See table for suggested antihypertensive medications by class (Table 2)
- 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

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: • *Suggestion:* Calcium-channel blocker Escalate dose of medication 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: • *Suggestion:* ACE-	Increase frequency of monitoring until stabilized	Do not hold cediranib unless otherwise clinically necessary

		inhibitor **Study drug does not need to be held unless otherwise clinically necessary** *Consider renal consult*		
Grade 3	Requiring more than one drug or more intensive therapy than previously.	Maximize 2 drug regimen • *Suggestions:* Calcium channel blocker + ACE-inhibitor Escalate doses of existing medication until BP is controlled or at a maximum dose. **Study Drug will not be held during trial of two drug combinations. Additional anti-hypertensive drugs, up to a total of 4, may be maximized for blood pressure control.**	Increased frequency of monitoring until stabilized	Do not hold cediranib unless BP is not decreased to less than 150/100 mmHg 48 hours after multi-drug therapy is instituted or if clinical symptoms worsen (e.g. headache). If BP is not controlled to less than 150/100 mmHg with maximal therapy or if clinical symptoms worsen, then hold drug (up to 14 days) until maximum effect of the anti-hypertensive agents is achieved. If BP is reduced to Grade 1 within 14 days, cediranib may be resumed at prior dose.
Grade 4	If threatening consequences OR SBP ≥ 180mmHg OR DBP ≥ 110mmHg	Initiate treatment Hospitalize patient for ICU management, IV therapy as necessary 14 days are allowed to maximize the full effect of anti-hypertensive agents.	Intensive BP monitoring (hospitalization if necessary)	**Hold cediranib.** If BP is reduced to Grade 1 within 14 days, cediranib may be resumed at a reduced dose.

Notes:

- 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 adverse event.
- Decisions to hold or decrease the cediranib dose during treatment must be based on BP

readings taken in the clinic by a medical professional.

Table 2 provides a suggested management guide to cediranib-induced hypertension as well as recommended anti-hypertensive medications depending on hepatic metabolism.

Table 2: Suggested Anti-hypertensive Medications, Starting Doses and Hepatic Metabolism

Dihydropyridine calcium-channel blockers (DHP CCB) (recommended as a first line agent for the management of HTN associated with cediranib unless contraindicated):

Agent	Initial Dose	Intermediate Dose	Maximum Dose	Hepatic Metabolism
Nifedipine XL	30 mg po qd	60 mg po qd	90 mg po qd	CYP 3A4 substrate
Amlodipine	2.5 mg po qd	5 mg po qd	10 mg po qd	CYP 3A4 substrate
Felodipine	2.5 mg po qd	5 mg po qd	10 mg po qd	CYP 3A4 substrate + inhibitor

Selective β blockers (BB):

Agent	Initial Dose	Intermediate Dose	Maximum Dose	Hepatic Metabolism
Metoprolol	25 mg po bid	50 mg po bid	100 mg po bid	CYP 2D6 substrate
Atenolol	25 mg po qd	50 mg po qd	100 mg po qd	**No**
Acebutolol	100 mg po bid	200mg-300 mg po bid	400 mg po bid	Yes (CYP450 unknown)
Bisoprolol	2.5 mg po qd	5-10 mg po bid	20 mg po qd	Yes(CYP450 unknown)

Angiotensin Converting Enzyme Inhibitors (ACEIs):

Agent	Initial Dose	Intermediate Dose	Maximum Dose	Hepatic Metabolism
Captopril	12.5 po tid	25 mg po tid	50 mg po tid	CYP 2D6

				substrate
Enalapril	5 mg po qd	10-20 mg po qd	40 mg po qd	CYP 3A4 substrate
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd	Yes (CYP450 unknown)
Lisinopril	5 mg po qd	10-20 mg po qd	40 mg po qd	**No**
Fosinopril	10 mg po qd	20 mg po qd	40 mg po qd	Yes (CYP450 unknown)
Rarely used: **Perindopril**	4mg po qd	none	8mg po qd	Yes but not CYP450
Quinapril	10mg po qd	20 mg po qd	40 mg po /qd	**No**
Angiotensin II Receptor Blockers (ARB's):				
Agent	Initial Dose	Intermediate Dose	Maximum Dose	Hepatic Metabolism
Losartan	25mg po qd	50 mg po qd	100 mg po qd	CYP 3A4 substrate
Candesartan	4mg po qd	8-16 mg po qd	32mg po qd	CYP 2C9 substrate
Irbesartan	75mg po qd	150 mg po qd	300 mg po qd	CYP 2C9 substrate
Telmisartan	40 mg po qd	none	80 mg po qd	**Yes but not CYP450**
Valsartan	80 mg po qd	none	160mg po qd	**Yes but not CYP450**
α and β blockers:				
Agent	Initial Dose	Intermediate Dose	Maximum Dose	Hepatic Metabolism
Labetolol	100 mg po bid	200 mg po bid	400 mg po bid	CYP 2D6 substrate and inhibitor

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with cediranib through CYP450.

** **Calcium channel blockers** are the recommended first line agent, unless contraindicated, for the management of hypertension associated with cediranib.

6.3.3. Management of Proteinuria

Proteinuria has been observed in cediranib studies. Increases in proteinuria may occur during treatment and should be managed as follows:

Proteinuria Value if following by U/A	Monitoring	Dose modification
Greater than 1+ on urine dipstick or U/A	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 ≤ 2.0	Perform UPC prior to each cycle.	Hold cediranib for up to 7 days and repeat UPC. If UPC resolves to ≤1.0, cediranib may be resumed at prior dose level. If UPC remains ≥1.0 g but ≤2.0 on repeat collection at least 7 days later, then resume treatment with reduction in cediranib by one dose level as per Table 6.2.1. Consider consultation with nephrologist.

UPC > 2.0	Perform UPC weekly until UPC is ≤2.0. Perform UPC prior to each cycle.	**Hold cediranib**. Consider consultation with nephrologist. When UPC is ≤2.0, resume treatment at one lower dose level for cediranib.

6.3.4. Decrease in LVEF

Patients who have any of the following should undergo an echocardiogram or MUGA at baseline and every four cycles while on study:

1. Prior treatment with anthracyclines
2. Prior treatment with trastuzumab
3. A New York Heart Association classification of II controlled with treatment (see Appendix E)
4. Prior central thoracic radiation therapy (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:

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

6.3.5. 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 16mg 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 6.3.1

6.3.6. Management of Fever and Neutropenia

Patients who develop fever and neutropenia will be managed via standard medical practice and American Society of Clinical Oncology and NCCN guidelines. Patients will need to recover from fever and active infectious issues prior to resuming therapy. Growth factors such as Neupogen or Neulasta may not be used.

6.3.7. Thyroid Toxicities

The use of cediranib has been associated with elevations of the thyroid stimulating hormone (TSH) and patients should be managed as per the following 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.

6.3.8. Dose Modifications for Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cediranib should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Cediranib should be discontinued upon diagnosis of RPLS. After consultation with the Principal Investigator and the NCI, consideration of restarting the study may be evaluated in light of any clinical benefit.

6.3.9. 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	Obtain shoulder MRI if not previously obtained.	Hold cediranib and olaparib for up to 14 days

	intervention indicated; limiting age appropriate instrumental ADL	If rotator cuff injury present on MRI, refer for physical therapy. Consider referral to orthopedics for evaluation as appropriate.	until symptoms resolve to Grade 1 or less. Cediranib and olaparib may then be resumed at a reduced dose level of each study drug. If patient is on the lowest dose level(s) of cediranib or olaparib, please contact the study PI to discuss dose modifications.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Obtain shoulder MRI if not previously obtained. Refer to orthopedic surgeon for evaluation.	Hold cediranib and olaparib for up to 14 days until symptoms resolve to Grade 1 or less. Cediranib and olaparib may then be resumed at a reduced dose level of each study drug after discussion with the overall PI.

6.3.10. Additional Toxicities and Dose Adjustments

Other toxicities are possible on this trial. In the phase 2 component, patients developing drug associated grade 3 or 4 non-hematological or non-mucosal toxicities that do not resolve or improve to grade 1 within 14 days will be removed from protocol. Dose modifications should be made as outlined in Section 6.3.1 of the protocol.

7. DRUG FORMULATION AND ADMINISTRATION

7.1. Cediranib (AZD2171, NSC 732208)

Please refer to the Investigator's Brochure for cediranib information in addition to the information below

7.1.1. Description

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

Other Names: AZD2171 maleate, cediranib, Recentin™

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

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

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

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

7.1.2. Form

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

In addition to the active ingredient, the tablets contain mannitol, dibasic calcium phosphate anhydrous, sodium starch glycolate, microcrystalline cellulose, and magnesium stearate with a film coat coating hypromellose 606, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide.

7.1.3. Route of Administration

Oral. Cediranib tablets should be taken either 1 hour before or 2 hours after meals.

7.1.4. Storage and Stability

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

Stability: Stability studies are ongoing.

7.1.5. Compatibility

From available preclinical data, there are no data suggesting clinically relevant pharmacokinetic interactions between cediranib and olaparib.

7.1.6. Availability

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

Cediranib is provided to the NCI under a Collaborative Agreement between AstraZeneca International and the DCTD, NCI (see Section 13).

7.1.7. Ordering

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

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

7.1.8. Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage or to obtain a copy of the DARF.)

7.1.9. 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 at IBCoordinator@mail.nih.gov.

7.1.10. Destruction and Return

Standard NCI return procedures will be followed.

7.2. Olaparib (AZD2281, NSC 747856)

Please refer to the Investigator's Brochure for olaparib information in addition to the information below. The Investigator's Brochure and all updates for olaparib will be provided to the overall Principal Investigator by AstraZeneca. Co-investigators may obtain a copy of the Investigator's Brochure for olaparib by contacting the overall Principal Investigator.

7.2.1. Description

Chemical Name:	4-[3-(Cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluro-benzyl]-2-H-phthalazin-1-one
Other Names:	AZD2281, KU-0059436; CO-CE 42; PARPi; olaparib
CAS Registry Number:	763113-22-0
Molecular Formula:	$C_{24}H_{23}FN_4O_3$
Molecular Weight:	434.47
Approximate Solubility:	Olaparib is freely soluble in dimethylsulphoxide (DMSO) and 1-methyl-2-pyrrolidinone (NMP), sparingly soluble in ethanol and methanol, and only very slightly soluble in water (<0.25 mg/mL).

7.2.2. Form

Olaparib capsules will be supplied as 50mg capsules. Each bottle contains 120 capsules. The capsules are Vcaps®Hydroxylpropyl Methylcellulose (HPMC) Capsugel® Capsules, not band-sealed or enteric-coated. Capsules may or may not be printed with a black ink radial logo (band) on the cap and body.

In addition to the active ingredient, the capsules contain Gelucire® 44/14 and Lauroyl macrogolglycerides. Olaparib capsules will be provided in white, high density polyethylene (HDPE) containers with child-resistant and tamper-evidence closure.

Olaparib tablets are green, film-coated tablets available in 25 mg, 100 mg, and 150 mg strengths. Tablets are packaged in induction-sealed high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle contains 32 tablets with dessicant.

Tablet core consists of olaparib, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. Tablet film-coating consists of hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black.

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.

7.2.3. Route of Administration

Oral. Olaparib capsules or tablets should be taken either 1 hour before or 2 hours after meals.

7.2.4. Storage and Stability

Storage: Store the olaparib capsules and tablets below 30°C.

Stability: Stability studies are ongoing.

7.2.5. Compatibility

From available preclinical data, there are no data suggesting clinically relevant pharmacokinetic interactions between cediranib and olaparib.

7.2.6. Availability and Ordering

AZD2281 (NSC 747856) may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated.

PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing

(OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

7.2.7. Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage or to obtain a copy of the DARF.)

7.2.8. 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 at IBCoordinator@mail.nih.gov.

7.2.9. Destruction and Return

Standard NCI return procedures will be followed.

8. CORRELATIVE/SPECIAL STUDIES

8.1. Tissue and Sample Acquisition and Processing

PBMC	Whole Blood	Plasma	Tumor/Effusion Cells	Imaging
PAR incorporation	CEC	Cytokines	IHC for γH2AX, RAD51, VEGF	K_{trans} and K_{ep}
SNP analysis			Tissue lysate array for angiogenesis and DNA repair endpoints	

All samples will be prioritized for the outlined translational endpoints. Should additional tissue or samples be available after completion of the stated endpoints, it may be used for additional research analysis with appropriate IRB approval or released at the patient's request for patient-requested assays.

8.2. Rationale for Selected Endpoints

These endpoints were selected to allow illustration of mechanism of the agents and potential interaction between the agents. They were also selected to investigate, in an exploratory fashion, whether any measures were predictive or prognostic, with the former being of greater interest.

8.3. Sample Acquisition

Patient Protections

- Each patient sample set will be coded with a unique patient identifier. No patient specific information is encoded in this ID. The protocol scientific investigator(s) handling the samples will be blinded as to the patient identification, patient data and outcome.
- Blood samples obtained by and stored through the Clinical Pharmacology Core will be labeled with unique barcodes.

Tumor Samples

- **Biopsies:** At least two core biopsies representing 18-gauge x at least 1cm in length, will be obtained. Inability to get tissue with a reasonable attempt will not preclude treatment and the patient will remain eligible for all other translational endpoints. Should CT scans be needed for safe core biopsy, a limit of 10 slices for each procedure will be observed to minimize radiation exposure to the patient.
- **Skin:** Where subcutaneous or skin is involved, two 2-3mm full thickness punch biopsies may be obtained.
- **Malignant effusions:** Known malignant effusions (pleural or peritoneal) may be acquired as the tissue sample in lieu of core tissue biopsies. Where both are present, the decision as to which sample to obtain will be made jointly between the patient, interventional radiology, and the research team.

Tumor Sample Handling

- **Core needles biopsy** samples are to be immediately embedded and frozen in OCT on dry ice on site and stored in liquid nitrogen until use. Biopsy scheduling and acquisition of research samples will follow the standard procedures for Special Procedures/Interventional Radiology and research sampling subjects protection. Members of the Kohn lab will be on call to receive, label, embed, and store biopsies Phone: beeper 102-11155.
- **Skin biopsies** will be embedded in OCT on site upon receipt, frozen in dry ice, and stored in liquid nitrogen until use. Members of the Kohn lab will be on call to receive, label, embed, and store biopsies Phone: beeper 102-11155.
- **Malignant Effusions:** A minimum of 50ml of non-heparanized effusion will be picked up by the Kohn laboratory. Ten aliquots of supernatant and 10 viably frozen cell pellets will be stored in liquid nitrogen until use.

Blood Sample Requirements

- **Circulating Endothelial Cells (CEC):** Three 8 cc CPT-citrate tubes (Tiger top: blue and black top) will be drawn pretreatment and the day of repeat imaging and biopsy. The Trepel laboratory (Dr. Min-Jung Lee, leemin@mail.nih.gov) will be contacted to confirm scheduling and will be called 301-496-1547 when the sample is ready. The sample is to be kept at room temperature until pick up.
- **Circulating Cytokines:** An approx 8-10ml clot tube and an 7 ml green top (heparin) tube (or volume equivalents) will be obtained prior to treatment and the day of repeat imaging and biopsy. The tubes will be packed on wet ice and picked up by the Clinical Pharmacology Core (102-11964 (Call 301-402-3622 – Kathy Compton with any questions). Serum and plasma will be separated and aliquoted according to the CPC SOPs and stored, barcoded, in the CPC repository until use.
- **PBMC PAR Incorporation:** Three 8 ml CPT-citrate tubes (Tiger top) will be obtained prior to treatment and the day of repeat imaging and biopsy. PBMCs will be isolated according to CPC SOP, aliquoted and stored, barcoded, in the CPC repository until use (102-11964 (Call 301-402-3622 – Kathy Compton with any questions).
- **Pharmacogenomics:** A single purple top tube (EDTA – minimum of 7 cc) will be collected prior to initiation of therapy. Sample will be placed on wet ice and refrigerated. The CPC will be paged for pickup at 102-11964 (Call 301-402-3622 – Kathy Compton with any questions). DNA extraction and analysis will follow the CPC pharmacogenomics SOPs.

8.4. Functional Imaging

- Patients will be scheduled with the Molecular Imaging Program of the Center for Cancer Research, NCI. No special preparation is required with the exception of recent electrolyte results and placement of a venous access device.
- Index lesions will be selected for serial measurement based on size (preferably at least 2 cm in largest diameter) and relative immobility. Scans will be obtained on the same schedule as the tumor biopsies.

- Conventional T1 and T2 weighted images of the target lesion will be obtained and a T1 map will be generated. This will be followed by a series of 3D gradient echo T1 weighted dynamic sequence which will be acquired before, during and after the administration of 0.1mmol/kg of a gadolinium chelate. Approximately 6 images are obtained prior to the administration of contrast media and the data collection continues of 5 minutes after injection. Data is transferred to an independent workstation and will be analyzed using a modified general kinetic model. This model generates two parameters K_{trans} and k_{ep} (permeability terms) which will be used as continuous outcome variables in the analysis. Vascular fraction may also be assessed. Color maps based on these parameters will also be generated. Data obtained before and on therapy will be compared for changes as a result of decreases in angiogenesis.

8.5. PAR Incorporation

A validated commercial PAR ELISA (Trevigen) will be used to quantitate PAR labeling in batched PBMC aliquots.

8.6. Circulating Endothelial Cells (CEC)

CEC and circulating endothelial precursors (CEP) will be analyzed by multi-parameter flow cytometry. Cells will be analyzed for forward and side scatter, and a dump channel will be created to exclude cells expressing hematopoietic markers, such as CD45. Endothelial cells will be identified using co-expression of markers, such as CD31 and CD146 for mature endothelial cells, and CD133 for CEP cells. The cell populations will also be analyzed for viability using scatter profiles and a vital stain, such as Hoechst 33258. Percentages of stained cells will be determined and compared with appropriate negative controls. Multi-parameter flow analysis will be performed with a BD LSR II equipped with FlowJo software, using a minimum of 500,000 events per analysis in the Trepel Laboratory.

8.7. Circulating Cytokines

VEGF, IL6, and IL8, among other pro-angiogenic cytokines have been shown to be induced during anti-angiogenic therapy as a pharmacodynamic measure of angiogenesis inhibition, including in cediranib in several cancers. Plasma will be collected and rapidly separated and stored. Samples will be batched and cytokines measured in at least duplicate using commercially available ELISA kits (most are available from R&D). A minimum of the following cytokines will be examined: VEGF, IL6, IL8. Others that may be considered include but are not limited to: sVEGFR2, Ang2, PIGF.

8.8. Pharmacogenomics, PARP and XRCC1 Polymorphisms

Multiple polymorphisms of the PARP-1 protein have been described (Cottet et al., 2000; Hur et al., 2006) and are listed in the SNP database of the NCBI (National Center for Biotechnology Information). Peripheral leukocytes will be genotyped for PARP polymorphisms in the CPC with Dr. W. D. Figg's laboratory. Particular attention will be given to the SNP, PARP1

Val762Ala, in which the variant allele contributes to dramatically lower PARP1 activity (Zhang et al. 2005). In addition, polymorphisms in XRCC1 will be assessed, as over-expression of XRCC1 decreases PARP1 activity. The SNP XRCC1 Arg399Glu resides in PARP1-interaction region (amino acid 314-402) in XRCC1 gene and Arg194Trp and Arg280Ile are correlated to altered risks to cancers and/or platinum sensitivity (Yuan et al., 2006; Skjelbred et al. 2006; Hao et al., 2004), though with inconsistent results (Zhai et al. 2006; Miao et al. 2006).

8.9. **IHC/IF**

Tumor samples (core biopsy recuts and/or effusion cell pellets) will be used for IHC or immunofluorescence (IF) to examine both vascular and DNA repair endpoints using validated SOPs. Scoring will be based upon number of positive cells and/or number of foci as pertinent to the endpoint. The following endpoints will be examined, with the following prioritization:

- RAD51 (foci per cell)
- γH2AX (foci per cell)
- VEGF
- CD31 or other measure of microvessels
- Pending tissue, some or all of the following may be examined: PARP1, BRCA1, ERCC1, XRCC1, other related endpoints.

8.10. **Proteomic Endpoints**

Core biopsy or effusion cell pellets will be examined in a blinded fashion in the fee-for-service MD Anderson Reverse Phase Protein Array Core. This provides a comprehensive analysis of total and phosphorylated proteins involved in invasion, cell cycle, proliferation, DNA repair. Data will be analyzed for change over time trends, as well as patterns of protein expression. These endpoints coupled with the IHC/IF results are aimed to evaluate HR competence (RAD51+) and changes in vascular signaling.

8.11. **BRCA Mutation Status**

No testing of BRCA mutation status is currently planned; however, research assessment of homologous recombination competence and endpoints in DNA damage repair pathways may be performed on available samples pending funding either within the NCI or with a collaborative partner outside of the NCI.

8.12. **Family Risk Assessment**

All patients will be asked to fill out the family risk assessment form (Appendix I). Where mutation is unknown, BRCAPro score will be calculated. This will be examined as a variable against outcome and HRD status in the translational endpoints.

8.13. **Post-progression Tissue Analysis**

At the time of progression, where possible, core needle biopsies from a new lesion or site of progression will be obtained. The biopsy will be taken at the time of drug discontinuation or within the 30d follow up period pending patient consent. This research biopsy will be optional and performed only if there is minimal risk. In BRCA mutation carriers, research sequencing of BRCA will be performed from the tissue to test for the presence of secondary mutations that can restore BRCA function, as well as the presence of other proteins (e.g. 53BP1), identified as potentially mediating PARP-inhibitor resistance. Pending tissue availability, other markers of DNA repair and vascular endpoints such (e.g. RAD51, γH2AX, VEGFR, CD31) will also be examined.

8.14. **Pharmacokinetic (PK) studies**

The steady-state plasma pharmacokinetics of cediranib and olaparib will be defined in a group of 12 patients in the safety expansion cohort treated with the recommended phase II doses of the combination, cediranib 30 mg QD and olaparib 200 mg BID, to assess whether or not the pharmacokinetic behavior of the two drugs is altered by their concurrent administration. Pharmacokinetic sampling will be performed during a single 24 h dosing interval after steady-state pharmacokinetic conditions for the repeated oral dosing schedules have been achieved when each agent is given alone (cycle 0) and again when given together in the same patient (cycle 1). In cycle 0, one group of six patients will receive single agent cediranib p.o. once daily for 7 days and the other group of six patients will receive single agent olaparib p.o. twice daily for 7 days. Pharmacokinetic samples will be collected on day 7 before and for 8 h after the dose is taken in the morning and before dosing on day 8. Combination therapy will begin on day 8 which is formally day 1 of cycle 1. Pharmacokinetic samples will again be collected before and for 8 hr after dosing on days 15-16 after the patients have received 14 days of combined therapy, as per the timepoints outlined below.

The sampling schedule has been devised to accommodate treatment on an outpatient basis. Patients will be instructed to take the doses of the two drugs as per outlined in the protocol at the same time every day during the pharmacokinetic study. Cediranib will be taken first thing in the morning on an empty stomach. One hour later, the patient may have a light meal, followed by the morning dose of olaparib. Dosing should be scheduled for times that will allow the patient to arrive at the clinic to obtain pharmacokinetic samples before dosing and to remain for an additional 8 hours after the morning dose of olaparib. The second daily dose of olaparib should be taken 12.0 ± 0.25 h after the morning dose. It is very important that the patient is aware that the morning doses of the two drugs on day 8 and day 16 must not be taken before arriving at the clinic and the 24.0 h pharmacokinetic sample has been collected. The first set of blood samples (6 mL) will be obtained during cycle 0 shortly before taking the day 7 dose of the single agent drug and at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 24.0 h after dosing.

The second set of blood samples (6 mL) will be obtained during cycle 1 starting on day 15 with the following schedule, to accommodate the sequential dosing schedule of the two drugs:

PK specimen	Day	Timing
#1	Cycle 1 Day 15	Just prior to cediranib dose
#2	Cycle 1 Day 15	0.5 hrs after cediranib dose
#3	Cycle 1 Day 15	1.0 hrs after cediranib dose
#4	Cycle 1 Day 15	2.0 hrs after cediranib dose, just prior to olaparib dose
#5	Cycle 1 Day 15	2.5 hrs after cediranib dose (= 0.5 hrs after olaparib dose)
#6	Cycle 1 Day 15	3.0 hrs after cediranib dose (= 1.0 hrs after olaparib dose)
#7	Cycle 1 Day 15	4.0 hrs after cediranib dose (= 2.0 hrs after olaparib dose)
#8	Cycle 1 Day 15	5.0 hrs after cediranib dose (= 3.0 hrs after olaparib dose)
#9	Cycle 1 Day 15	6.0 hrs after cediranib dose (= 4.0 hrs after olaparib dose)
#10	Cycle 1 Day 15	8.0 hrs after cediranib dose (= 6.0 hrs after olaparib dose)
#11	Cycle 1 Day 16	24.0 hrs after C1D15 cediranib dose, just prior to C1D16 cediranib dose
#12	Cycle 1 Day 16	24.0 hrs after C1D15 morning olaparib odse, just prior to C1D16 morning olaparib dose

Samples will be collected in plastic green stoppered Vacutainer 6.0 mL plasma collection tubes with spray-coated sodium heparin, gently inverted 5-times to thoroughly mix the blood with the anticoagulant, and placed on wet ice until centrifuged (1,300 x g, 10 min, 4°C) within 15 min after collection. Separate the plasma from the blood cells using a disposable pipette and transfer the plasma into a 4.5 mL self-standing polypropylene cryogenic storage vial with external threads (Fisher Scientific, cat. no. 12-565-291). Affix a pre-printed label, with the protocol number, patient accession number, and sample number onto the cryovial, oriented crosswise toward the upper part of the tube, without overlapping the vial cap. Completely cover the label with polyester protective label tape (Fisher Scientific, cat. no. 11-867B) to prevent the label from detaching from the vial when stored frozen. Store the plasma samples in a freezer at <-70°C until packaged for shipment to the analytical laboratory.

Send complete sets of samples from one or more patients by next day delivery to the address listed below. Place the sample tubes in a zip lock plastic bag. Package samples in a seamless styrofoam container. Place the sample bag over at least 3-4 inches of dry ice on the bottom of the container and completely cover with an additional 3-4 inches or more of dry-ice. Seal the styrofoam container within a tight-fitting cardboard shipping box. Insert copies of the Pharmacokinetic Data Form for each set of samples into a separate zip-lock plastic bag placed on top of the styrofoam container before the external shipping box is sealed. Send the samples from Monday to Wednesday by overnight courier for delivery by 10 a.m. on the following day. Samples should not be shipped on a Thursday or Friday. Please provide notification of the sample shipment by e-mail to shipping to jsupko@partners.org and slhilderbrand@partners.org.

Dr. Jeffrey G. Supko
Massachusetts General Hospital
55 Fruit St., GRJ 1025
Boston, MA 02114
Tel: 617-724-1970

The concentration of cediranib and olaparib in the plasma samples will be determined by the DF/HCC Cancer Pharmacology Core laboratory located on the main campus of the Massachusetts General Hospital (Boston, MA). An analytical method facilitating the concurrent determination of the two drugs based upon for both compounds based upon high performance liquid chromatography with tandem mass spectrometric detection has been developed. The analytical methods will be validated and applied to the analysis of study samples as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 (http://www.fda.gov/-downloads/Drugs/Guidances/ucm070107.pdf).

Individual patient plasma concentration-time curves will be analyzed by noncompartmental methods using routines supplied in the WinNonlin Professional Version 5.0.1 software package (Pharsight Corp., Cary, NC). Pharmacokinetic parameters and variables will be calculated according to standard equations. Mean values of pharmacokinetic parameters will be statistically compared using the paired two-tailed t-test of the log-transformed data.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and assessment of cardiac function must be done $\leq$ 4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted. After completion of the first two cycles, cycle visits and associated studies can be performed within $\pm$ 7 days of the protocol-specified date, unless otherwise noted. The study calendar for the Phase I and II portions of the study are as per the following pages:

9.1. Study Calendar: Phase I and Phase I-T

	Pre-Study	Prior to Each Cycle[a,o]	Cycles 1 & 2 Day 8, 15, 22 (+/- 3 days)	Every 2 Cycles	Off Treatment
Informed Consent[a]	X[a]				
Medical History	X				
Concomitant Medications[b]	X[b]	X[b]	X[b]		X[b]
Adverse Event Assessment		X	X		X
Vital Signs[c]	X[c]	X[c]	X[c]		X[c]
BP Measurement at Home (See Appendix C)		Twice a day while on study			
Physical Exam	X	X	X		X
Height	X				X
Weight	X	X			
ECOG Performance Status[d]	X[d]	X[d]			X[d]
CBC with Differential	X	X	X		X
Serum Chemistry[e]	X[e]	X[e]	X[e]		X[e]
INR and PTT	X				
Troponin T or I TSH and Free T4[f]	X[f]	X[f]			X[f]
Urinalysis[g]	X[g]	X[g]	X[g]		X[g]
Electrocardiogram	X	X[h]			
MUGA or Echocardiogram[i]	X			X	
Pregnancy Test[j]	X[j]				
CA-125 Measurements[k]	X[k]	X[k]			
Tumor Measurements[l,m]	X[l]			X[l,m]	
Review of BP diary by study team		X	X		
Pharmacokinetics [p]		X	X		

a: Informed consent will be obtained prior to any study-related screening tests. For Cycle 1 Day 1, physical examination and laboratory evaluations do not have to be repeated if they have been performed at screening within 7 days of Cycle 1 Day 1.
b: Because of a potential for interaction of cediranib and olaparib with other drugs through the cytochrome P450 system, the Principal Investigator should be alerted if the patient is taking any other medications known to affect P450 isoenzymes.
c: Temperature, pulse, blood pressure
d: See Appendix A for ECOG performance status
e: Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, phosphorus, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, LDH.
f: Pre-study and prior to the first 2 cycles, then as clinically indicated, and at off-study visit.
g: A urine protein:creatinine ratio may be used instead. See Section 6.3.3 Management of Proteinuria if dipstick at least 1+ on study.
h: ECG done prior to Cycle 1 and 2, and then prior to every cycle if clinically indicated.

i: MUGA or echocardiogram should be done at baseline and every other cycle for those patients at increased risk for compromised LVEF. Increased risk patients have had one or more of the following: (1) prior treatment with anthracyclines, (2) prior treatment with trastuzumab, (3) NY Heart Association classification of II, (4) prior central thoracic RT, (5) history of myocardial infarction within the 12 months prior.

j: beta-HCG for women of childbearing potential.

k: If patients have no measurable cancer for RECIST assessment, the patient must have two pretreatment CA-125 samples that are at least twice the upper limit of normal (at least 1 day but not more than 3 months apart; at least one of the samples should be within 1 week of starting treatment). A CA-125 level drawn just prior (within 1 week of) to Cycle 1 Day 1 of cediranib/olaparib dosing will be used as the BASELINE CA-125. CA-125 will be drawn at the start of each cycle.

l: Tumor measurements by CT scans or MRI will be performed within the 4 weeks prior to starting cediranib/olaparib and will be performed after every 8 weeks (+/- 1 week) of treatment. If a partial or complete response is noted, a confirmatory CT scan or MRI should be performed. The next planned restaging CT scan or MRI may be used as the confirmatory scan.

m: For patients in the Phase 1 portion of the trial who have been on trial for greater than 1 year without evidence of disease progression, the treating investigator may choose to decrease the frequency of re-staging CT scans to once every 4 cycles.

o: For patients in the Phase 1 portion of the trial who have been on trial for greater than 3 years without evidence of disease progression, the treating investigator may choose to decrease the frequency of visits to once every 2 cycles. These patients should have CBC with differential, serum chemistry, and urine protein assessment (UPC or urinalysis) performed and con-meds, adverse events, and blood pressure diary should be reviewed in-person or by telephone with the study team, but all other assessments may be omitted.

p: Reference section 8.14 of the protocol for further information on exact timing requirements of samples.

9.2. Study Calendar: Phase II

	Pre-Study[a]	Prior to Each Cycle[a,r]	Cycles 1&2 Weekly[b]	Cycles 1&2 Day 15 (+/- 3 days)	Every 2 Cycles	Every 4 Cycles	Off Treatment[p]
Informed Consent[a]	X[a]						
Medical History	X						
Concomitant Medications[c]	X[c]	X[c]	X[c]				X[c]
Adverse Event Assessment		X	X[b]				X
Vital Signs[d]	X[d]	X[d]					X[d]
BP Measurement at Home[e] (See Appendix C)		Twice a day while on study					
Physical Exam	X	X					X
Height	X						X
Weight	X	X					
ECOG Performance Status[f]	X[f]	X[f]					X[f]
CBC with Differential	X	X		X			X
Serum Chemistry[g]	X[g]	X[g]		X[g]			X[g]
INR and PTT	X						
Troponin T or I TSH and Free T4[h]	X[h]	X[h]					X
Urinalysis[i]	X[i]	X[i]		X[i]			X[i]
Electrocardiogram	X[j]	X[j]					
MUGA or Echocardiogram[k]	X					X	
Pregnancy Test[l]	X[l]						
CA-125 Measurements	X	X					X
Tumor Measurements[m,q]	X[m]				X[l,q]		
Family Risk Assessment	X[n]						
Translational Studies	X[o]						

a: Informed consent will be obtained prior to any study-related screening tests and within 4 weeks of starting study drug. For Cycle 1 Day 1, physical examination, laboratory evaluations, and EKG do not have to be repeated if they have been performed at screening within 7 days of Cycle 1 Day 1.

b: Participants should be contacted at least once weekly over the phone or be assessed in person for the first two cycles on study to assess for adverse events and concomitant medications. Pre-cycle and off-study AE assessments must be done at a scheduled clinic visit.

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

d: Temperature, pulse, blood pressure

e: Home blood pressure monitoring is only required for patients receiving cediranib

f: See Appendix A for ECOG performance status

g: Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, phosphorus, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin.

h: Pre-study, prior to the first 2 cycles, and at off-study visit for all participants. Otherwise, should be checked prior to each cycle if clinically indicated.

i: A urine protein:creatinine ratio may be used instead. See Section 6.3.3 Management of Proteinuria if dipstick at least 1+ on study.

j: ECG done prior to Cycle 1 and 2, and then prior to every cycle if clinically indicated. The pre-study ECG may be used as the Cycle 1 ECG if performed within 7 days of Cycle 1 Day 1.

k: MUGA or echocardiogram should be done at baseline and every 4 cycles for those patients at increased risk for compromised LVEF. Increased risk patients have had one or more of the following: (1) prior treatment with anthracyclines, (2) prior treatment with trastuzumab, (3) NY Heart Association classification of II, (4) prior central thoracic RT, (5) history of myocardial infarction within the 12 months prior.

l: beta-HCG for women of childbearing potential.

m: Tumor measurements by CT scans or MRI will be performed within the 4 weeks prior to starting cediranib/olaparib and will be performed after every 8 weeks (+/- 1 week) of treatment. If a partial or complete response is noted, a confirmatory CT scan or MRI should be performed. The next planned restaging CT scan or MRI may be used as the confirmatory scan. For patients in the Phase 2 portion of the trial, the frequency of restaging studies will decrease to once every 12 weeks (+/- 1 week) after the 20^{th} cycle of treatment.

n: The Family Risk Assessment questionnaire (Appendix I) should be completed by the patient and returned to the study staff by Cycle 2.

o: For patients opting to participate in translational studies at the NCI. Study schedules will be as per Section 5.1.4.

p: Off-treatment assessments should be performed within 30 days of stopping study treatment.

q: For patients in the Phase 2 portion of the trial who have been on trial for greater than 4 years without evidence of disease progression, the treating investigator may choose to decrease the frequency of re-staging CT scans to once every 4 cycles.

r: For patients in the Phase 2 portion of the trial who have been on trial for greater than 4 years without evidence of disease progression, the treating investigator may choose to decrease the frequency of visits to once every 2 cycles. These patients should have CBC with differential, serum chemistry, and urine protein assessment (UPC or urinalysis) performed and con-meds, adverse events, and blood pressure diary should be reviewed in-person or by telephone with the study team, but all other assessments may be omitted.

10. MEASUREMENT OF EFFECT

Response is not the primary endpoint of the phase I component of this trial. However, participants with measurable disease will be assessed by RECIST and those who do not have measurable cancer via clinical response benefit (modified GCIG CA-125 response or stable disease for at least 16 weeks). For the purposes of this study, participants should be reevaluated for disease response based upon how their disease is being assessed. If RECIST criteria apply, patients should undergo a repeat radiographic assessment every 8 weeks (+/- 1 week) with CT or MRI scans. For patients with only elevated CA125 values, modified GCIG CA125 response will be measured every 4 weeks (+/- 1 week). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response. The next planned restaging CT Scan or MRI may be used as the confirmatory scan.

10.1. Measurable Disease Response Definition

When measurable lesions are present, 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 only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

10.1.1. Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment with cediranib and olaparib.

Evaluable for objective response. Only those participants 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 participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

10.1.2. Disease Parameters

Measurable disease. Measurable disease are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10mm with calipers by clinical exam. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered 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 tht, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the nxt 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 the lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum parameters 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 or absence of each should be noted at each follow-up.

10.1.3. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or digital measurement tool. 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 when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10mm diameter as assessed using calipers

(e.g., skin nodules). For 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 5mm or less. If CT scans have slice thickness greater than 5mm, 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).

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 pathologic 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 will not be used to assess response for the phase II portion of this study. If markers are initially above the upper normal limit, they must normalize for a subject 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 Integroup 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]. CA-125 response criteria and progression criteria are detailed further in Section 10.2.

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.

10.1.4. Response Criteria

Evaluation of Target Lesions

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

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

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

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.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing, an overall assessment cannot be done. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum diameters of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

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

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

Progressive Disease (PD): Appearance of one or more new lesions (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: 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 review of the Principal Investigator (or Protocol Chair). Additionally, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is mandatory to differentiate between stable or progressive disease status.

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 participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥ 4 wks confirmation
CR	NonCR/Non-PD	No	PR	≥ 4 wks confirmation
CR	Not evaluated	No	PR	
PR	Non-PD/not evaluated	No	PR	
SD	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	

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

** Only for non-randomized trials with response as primary endpoint

Note: Participants 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.

10.2. CA-125 Response Definition

For patients enrolled in this study with no measurable cancer but elevated CA125 levels, these subjects enrolled will have CA-125 levels at least twice the upper limit of normal (see Section 3.1.2). The GCIG CA-125 response criteria (Rustin, 2003), which are a better prognostic tool than RECIST in second-line cytotoxic therapy of ovarian cancer (Gronlund *et al.*, 2004), will be

modified to assess CA-125 response to combination therapy with cediranib and olaparib. The original criteria were developed for the use of cytotoxic agents, which generally produce a rapid decline in CA-125 elevels in patients with chemosensitive disease. However, combination therapy with an anti-angiogenic and a PARP-inhibitor may produce either disease stability, due to its cytostatic nature, or disease response of a more gradual tempo, based on mechanism of action. Thus, it may take more time for CA-125 responses (and tumor measurement responses) to be seen with cediranib/olaparib combination therapy. Towards that end, we have modified the timing of response determination set out by the GCIG.

10.2.1. Baseline CA-125 Level for Response Assessment

Two pretreatment CA-125 samples must be at least twice the upper limit of normal (at least 1 day but not more than 3 months apart; at least one of the samples should be within 1 week of starting treatment). **A CA-125 level drawn just prior to (within 1 week of) Cycle 1 Day 1 will be used as the BASELINE CA-125.**

10.2.2. Definition of CA-125 Response

CA-125 levels will be drawn at the start of each cycle. A CA-125 response occurs if, after two elevated levels before therapy, a subsequent sample (taken at least 4 weeks +/- 1 week after initiating cediranib/olaparib) shows at least a 50% decrease that is confirmed by a sequential confirmatory sample (taken 4 weeks +/- 1 week after the prior sample). The confirmatory sample must be less than or equal to 110% of the prior sample showing a response.

10.2.3. Definition of CA-125 progression:

No validated definitions of CA-125 progression have been published to date. Given the potential cytostatic nature of angiogenesis inhibitors such as cediranib, in this trial the criterion for progression based on CA-125 level is: **doubling of the CA-125 level from BASELINE (pre-treatment).**

As long as interval CA-125 measurements are less than double the value from baseline, subjects may continue on study, provided that tumor measurements are stable as well, without the development of new lesions.

10.3. Response Criteria

Clinical response benefit is defined as:

a) For patients with only an elevated CA125 (no measurable cancer via radiographic test): Modified GCIG CA-125 response (see Section 10.2) without progressive disease on CT scan for at least 16 weeks

OR

b) For patients with measurable disease: Tumor response by RECIST criteria or stable disease for at least 16 weeks.

10.4. Confirmatory Measurement/Duration of Response

10.4.1. Confirmation

To be assigned a status of clinical response benefit, the modified GCIG CA-125 response criteria incorporate the need for a sequential confirmatory CA-125 level as described in Section 10.2.

For patients being followed with measurable disease, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are met. The next scheduled CT or MRI may be used as the confirmatory scan. In the case of SD, follow-up measurements must have met the SD criteria for at least 16 weeks, with scans every 8 weeks (+/- 1 week).

10.4.2. Duration of Overall Response

The duration of modified GCIG CA-125 response or RECIST assessment is measured from the time measurement criteria are met (see Section 10.1) until the first date that recurrent or progressive disease is objective documented by CA-125 level (taking as reference for progression of CA-125 the baseline measurement of CA-125 recorded pretreatment) or by progressive disease noted on CT scan by RECIST criteria.

10.4.3. 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 start, with stable disease of at least 16 weeks meeting the primary objective of the Phase II component.

10.4.4. Duration of Response

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

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent 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.

10.4.5. Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression.

10.4.6. Response Review

Radiology assessments for DF/HCC sites will be provided by the DF/HCC tumormetrics core. Assessment for other participating sites should be performed per local protocols. All complete or partial responses in patients with measurable disease should be confirmed by the DF/HCC tumormetrics core. Please see Appendix H for procedures for submission of materials for DF/HCC tumormetrics review from non-DF/HCC participating institutions.

10.5. Other Response Parameters

Criteria for CA-125 response can be found in Section 10.2.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1. General

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

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event or related to a study procedures and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11.2. Definitions

11.2.1. Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.2.2. Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;

- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures;
- elective or pre-planned treatment for a pre-existing condition that did not worsen;
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission;
- respite care.

11.2.3. Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

Expected Adverse Event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

Unexpected Adverse Event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.2.4. Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- 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.

11.3. Recording Adverse Events

Adverse event information will be obtained at each contact with the participant. All adverse events will be recorded on the appropriate study-specific case report forms (CRFs).

11.4. Reporting Adverse Events

Each adverse event will be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local policies, and federal guidelines and regulations as appropriate.

It is the responsibility of the participating investigator to notify the Principal Investigator (or Protocol Chair), IRB, and others of all serious adverse events as required in the protocol.

The Principal Investigator (or Protocol Chair) will provide information with respect to adverse events and safe use of the study treatment (e.g., safety reports, Action Letters) to all participating investigators as soon as the information becomes available.

11.5. Sponsor Notification by Investigator

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 11.5.3).

In the rare event when Internet connectivity is disrupted a 24-hour notifications is to be made to NCI by telephone at: 301-897-7497, or 301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

11.5.1. Expedited Reporting Guidelines

CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 1 Trials

Phase 1 Trials

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

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Phase 2 and 3 Trials

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	Without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.

- "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

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

11.5.2. Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events will be reported to the Principal Investigator (or Protocol Chair) on the toxicity Case Report Forms.

11.6. Institutional Review Board (IRB) Notification by Investigator

The participating investigator will report all adverse events and serious adverse events to the Principal Investigator (or Protocol Chair) and to the IRB according to the local IRB's policies and procedures in reporting adverse events.

In the event of a multi-center study, the Principal Investigator (or Protocol Chair) will report adverse events and serious adverse events from all participating sites to the DFCI IRB according to the IRB's policies and procedures in reporting adverse events.

11.7. Hospital Risk Management Notification by Investigator

The participating investigator will report to the Principal Investigator (or Protocol Chair) and to local Risk Management any subject safety reports or sentinel events that require reporting according to institutional policy.

12. DATA AND SAFETY MONITORING

12.1. Data Reporting

12.1.1. Method

The QACT will collect, manage, and monitor data for this study.

Additionally, this study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov/.

Note: All adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via CTMS or CDUS.

12.1.2. Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

Participating sites are responsible for submitting CDUS data and/or data forms quarterly by January 15, April 15, July 15, and October 15 to allow time for Coordinating Center compilation,

Principal Investigator review, and timely submission to CTEP (see Section 12.1.1.). For trials monitored by CTMS, the monthly data submission to CTEP from Theradex should be copied to the Coordinating Center.

The DF/HCC sites participating in this study are responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review. Data for non-DF/HCC institutions will be entered in CDUS by the lead institution.

12.2. **Safety Meetings**

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMB will meet every 6 months and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3. **Monitoring**

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1. Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2. Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3. Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- ICH Consolidated Good Clinical Practice: Guidelines (E6)
  www.fda.gov/cder/guidance/iche6.htm

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

  - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- Institutional research policies and procedures www.dfhcc.harvard.edu/clinical-research-support/clinical-research-operations-cro/policies-and-procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4. Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5. Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6. Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

CRADA INFORMATION

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as ”Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” (http://ctep.cancer.gov/industryCollaborations2/default.htm#guidelines_for_collaborations) 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 investigational 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 investigational 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 NIH, 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 investigational 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 investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order.. 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:

   E-mail: 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.

14. STATISTICAL CONSIDERATIONS

This is a Phase I/II trial to investigate the combination of cediranib and olaparib in recurrent high-grade papillary-serous or endometrioid ovarian, fallopian tube, or peritoneal cancer and in metastatic triple-negative breast cancer.

14.1. Study Design/Endpoints

14.1.1. Primary Objectives

1. **Phase 1 Component:** Determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of cediranib in combination with olaparib in the treatment of recurrent ovarian, fallopian tube, and peritoneal cancer or metastatic triple-negative breast cancer.

2. **Phase 2 Component:** Investigate the efficacy of cediranib in combination with olaparib (as determined by progression-free survival (PFS)) at the MTD / recommended phase 2 dose (RP2D) compared to that of olaparib alone in patients with recurrent platinum-sensitive grade 2 or 3 papillary-serous or endometrioid ovarian, fallopian tube, or peritoneal cancer.

3. **Phase 1-T (tablet) Component:** Determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of cediranib in combination with olaparib (tablet

formulation) in the treatment of recurrent ovarian, fallopian tube, and peritoneal cancer.

14.1.2. Secondary Objectives

1. **Phase 1 Component:** Assess the toxicities of the combination of cediranib and olaparib in the treatment of recurrent ovarian, fallopian tube, and peritoneal cancer or metastatic triple-negative breast cancer

2. **Phase 2 Component:** Investigate tumor response rate, clinical benefit rate (response or stable disease x 16 weeks, as determined by RECIST 1.1 criteria, and overall survival for patients with recurrent platinum-sensitive grade 2 or 3 papillary-serous or endometrioid ovarian, fallopian tube, or peritoneal cancer treated with cediranib and olaparib at the RP2D compared to cediranib alone.

3. **Phase 1-T (tablet) Component:** Assess the toxicities of the combination of cediranib and olaparib in the treatment of recurrent ovarian, fallopian tube, and peritoneal cancer.

14.1.3. Study Design

Phase 1 and Phase 1-T

The Phase 1 and Phase 1-T components of this trial will employ a 3+3 design, escalating on 0/3 or 1/6 DLT, and de-escalating if 2 DLTs are encountered. Please refer to Section 5.3 for more trial-specific escalation details.

Probabilities of dose escalation (based on a binomial distribution) are tabulated below for a series of assumed true toxicity rates:

True Toxicity Rate	0.1	0.2	0.3	0.4	0.5	0.6	0.65	0.7	0.8	0.9
Probability of Escalation	0.91	0.71	0.49	0.31	0.17	0.08	0.053	0.032	0.009	0.001

At least 6 patients will be treated at MTD, and no more than 1 patient should experience a DLT at the MTD level. Based on the exact binomial distribution, we would be unlikely to escalate the dose if the true toxicity was 65% or greater ($p = 0.053$).

When the MTD has been determined and confirmed in at least 6 patients, up to an additional 8 patients may be enrolled at the MTD dose to gain experience at the MTD dose level.

Phase 2

To assess the clinical efficacy of the combination of cediranib and olaparib, a randomized two-arm study will be conducted with cediranib and olaparib combined at the RP2D compared to olaparib alone. Patients will be randomized after stratification for prior receipt of anti-angiogenic therapy and BRCA status.

Phase 1-T pharmacokinetic (PK) Expansion
When the MTD has been determined and confirmed in at least 6 patients, two cohorts of 6 patients evaluable for PK purposes will be enrolled at the MTD in order to assess PK for the study drugs.

14.1.4. Primary Study Endpoints

Phase I: The primary study endpoint for the Phase I portion of this trial will be establishment of the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT). The MTD will then be considered the recommended Phase 2 dose (RP2D).

Phase II: The primary study endpoint for the Phase II portion of this trial will be progression-free survival.

Phase I-T: The primary study endpoint for the Phase I-T portion of this trial will be establishment of the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT) with cediranib and the tablet formulation of olaparib.

14.1.5. Secondary Study Endpoints

Phase I: Secondary endpoints will include assessing the toxicities of cediranib in combination with olaparib in patients with recurrent ovarian, fallopian tube, and peritoneal cancer or metastatic triple-negative breast cancer.

Phase II: Secondary endpoints will include assessing response rate (as defined by RECIST criteria) and clinical benefit rate (response + stable disease ≥ 16 weeks); and assessing overall survival.

Phase I-T: Secondary endpoints will include assessing the toxicities of cediranib in combination with olaparib (tablet formulation) in patients with recurrent ovarian, fallopian tube, and peritoneal cancer.

14.2. Sample Size and Data Analysis

The planned sample size will vary depending upon the number of patients accrued in the Phase I and Phase I-T components of the study. The Phase II component will randomize 90 patients (i.e., 45 patients in each arm). The Phase 1 component will be accrued at the DF/HCC and University of Chicago sites, with an anticipated accrual rate of 2 to 3 patients per month. The

Phase 1-T component will be accrued at the DF/HCC and NCI sites, with an anticipated accrual of 2 to 3 patients per month. We will plan on a multi-center accrual for the Phase 2 component of the study, with accrual planned to complete over an 18 month period.

The expected PFS to a platinum-based regimen in this setting is approximately 6 months (Markman *et al.*, 1991). The PFS observed with cediranib alone in this patient population was 5.2 months (Matulonis *et al.*, 2009). In the Phase II study of olaparib in BRCA mutation carriers, the estimated PFS ranged from approximately 2.5 months to 5.5 months between the 100mg BID and 400mg BID cohorts (Audeh *et al.*, 2010). In BRCA wild-type patients, the estimated response rate was 23.9% (Gelmon *et al.*, 2010), which is comparable to the 20% response rate observed with single-agent cediranib (Matulonis *et al.*, 2008). Given this similar activity and the observed data in the Audeh *et al.* Phase II trial, we therefore project a PFS in a control arm of olaparib alone to be similar to that of platinum-based regimens at 6 months. An increase in progression-free survival to 10.5 months (from the projected 6 months) would be considered of clinical interest. In the Phase II portion of the study, for a power of 86% to reject H_o: Median PFS in both arms = 6 months in favor of H_1: Median PFS of the group with olaparib combination > 10.5 months with an alpha of 0.10, 71 events (i.e., disease progressions) out of a total of 82 evaluable patients will be required to detect a hazard ratio of 0.5716 (experimental over control). We will therefore perform the final PFS analysis when the 71st evaluable patient experiences cancer progression. It is anticipated that 10% of subjects will not be evaluable, and thus the total number of subjects with platinum-sensitive disease to be enrolled in the Phase II portion of the study is 90. Progression-free survival will be evaluated by Kaplan-Meier analysis and Log-Rank test for between group comparison, and median survival times reported. To minimize the likelihood of exposing study patients to an inactive regimen, an interim assessment of the hazard ratio for disease progression (experimental over control) will be performed when the 36th patient experiences cancer progression. If the estimated hazard ratio at that time is 1 or greater, accrual to the study will be halted for futility.

Response rates with olaparib in patients with recurrent ovarian cancer have been reported at approximately 20% (Gelmon *et al.*, 2010). Second-line platinum results in a response rate of ~30% in patients who have had a treatment-free interval between 6 and 24 months. With an enrollment of 41 patients in each arm, there will be an 80% power to detect a difference in tumor response and clinical benefit rates as small as 29.5% with an alpha of 0.05. H_0: single-agent olaparib response rate = cediranib and olaparib response rate = 20%. H_1: cediranib and olaparib > 49.5%. The response rates will be compared by an exact test and 95% confidence intervals will also be reported.

The secondary endpoint of overall survival will also be evaluated by Kaplan-Meier analysis and Log-Rank test for between-group comparison, and median survival time will be reported.

14.3. **Reporting and Exclusions**

14.3.1. Evaluation of Toxicity

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

14.3.2. 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). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

All of the participants 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. Participants 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, and sometimes category 3, will be protocol specific.

All conclusions should be based on all eligible participants. Subanalyses may then be performed on the basis of a subset of participants, 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 participants from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

15. PUBLICATION PLAN

Publication guidelines exist within the DF/HCC Gynecologic Oncology Program. The study principal investigator will be responsible for collection of data, interpretation of data, monitoring of toxicities, and publication of abstracts and final manuscripts. The principal investigator chooses the different authorship slots per the DF/HCC gynecologic oncology program guidelines.

The results will be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three (3) years after the end of data collection.

16. REFERENCES

Audeh, M.W., J. Carmichael, R.T. Penson, *et al.* (2010) Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients iwth BRCA1 or BRCA2 mutations and recurrent ovarian cancer : a proof-of-concept trial. *Lancet* 376(9737) : 245-251.

Bradley, D.P., J.T. Tessier, D.R. Checkley, *et al.* (2004) The VEGF signaling inhibitors ZD6474 and AZD2171 compromise hemodynamic parameters in an SW620 human colon tumor model: An analysis using perfusion-permeability dynamic contrast-enhanced magnetic resonance imaging (*pp*-DCE-MRI). *Proc Am Assoc Cancer Res*: A4552.

Bryant, H.E., N. Schultz, H.D. Thomas, *et al.* (2005) Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 434(7035): 913-917.

Burger, R.A., M.V. Sill, B.J. Monk, *et al.* (2007) Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *J Clin Onc* 25(33): 5165-5171.

Cannistra, S., U.A. Matulonis, R.T. Penson, *et al.* (2007) Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Onc* 25(33): 5180-5186.

Drevs, J., J. Esser, S.R. Wedge, *et al.* (2004) Effect of AZD2171, a highly potent VEGF receptor tyrosine kinase inhibitor, on primary tumor growth, metastasis and vessel density in murine renal cell carcinoma. *Proc Am Assoc Cancer Res*: A4554.

Farmer, H., N. McCabe, C.J. Lord, *et al.* (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 434(7035): 917-921.

Fong, P.C., D.S. Boss, C.P. Carden, *et al.* (2008) AZD2281 (KU-0059436), a PARP (poly ADP-ribose polymerase) inhibitor with single agent anticancer activity in patients with BRCA deficient ovarian cancer: Results from a phase I study. *ASCO Proceedings* 26: 2008, Abstract 5510.

Gelmon, K.A., H.W. Hirte, A. Robidoux, *et al.* (2010) Can we define tumors that will respond to PARP inhibitors? A phase II correlative study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer. *ASCO Proceedings* 28: 2010, Abstract 3002.

Gronlund, B., C. Hogdall, J. Hilden, *et al.* (2004). Should CA-125 response criteria be preferred to response evaluation criteria in solid tumors (RECIST) for prognostication during second-line chemotherapy of ovarian carcinoma? *J Clin Onc* 22(20): 4051-4058.

Hennequin, L.F., A.P. Thomas, C. Johnstone, *et al.* (1999) Design and structure-activity relationship of a new class of potent VEGF receptor tyrosine kinase inhibitors. *J Med Chem*. 42:5369-5389.

Hirte, H.W., L. Vidal, G.F. Fleming, *et al.* (2008) A phase II study of cediranib (AZD2171) in recurrent or persistent ovarian, peritoneal or fallopian tube cancer. *ASCO Proceedings* 26:2008, Abstract 5521.

Hughes-Davies, L., D. Huntsman, M. Ruas *et al.* (2003) EMSY links the BRCA2 pathway to sporadic breast and ovarian cancer. *Cell* 115(5): 523-535.

Jemal, A., R. Siegel, E. Ward, *et al.* (2008) Cancer statistics, 2008. *CA Cancer J Clin* 58(2): 71-96.

Klinowska, T.C., J.A. Jackson, P.M. Farrington, *et al.* (2004) AZD2171, a highly potent inhibitor of VEGF receptor tyrosine kinase activity, inhibits the growth of spontaneous mammary tumors in the MMTV-neu transgenic mouse. *Proc Am Assoc Cancer Res*: A4540.

Lakhani, S.R., M.J. Van De Vijver, J. Jacquemier, *et al.* (2002) The pathology of familial breast cancer predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. *J Clin Onc* 20: 2310-2318.

Laurie, S.A., I. Gauthier, A. Arnold, *et al.* (2008) Phase I and pharmacokinetic study of daily oral AZD2171, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with carboplatin and paclitaxel in patients with advanced non-small-cell lung cancer: the National Cancer Institute of Canada Clinical Trials Group. *J Clin Onc* 26: 1871-1878.

Ledermann, J.A., P. Harter, C. Gourley, *et al.* (2011) Phase II randomized placebo-controlled study of olaparib (AZD2281) in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). *ASCO Proceedings* 29: Abstract 5003.

Markman, M., R. Rothman, T. Hakes, *et al.* (1991) Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Onc* 9(3): 389-393.

Matulonis, U.A., S.T. Berlin, C.N. Krasner, *et al.* (2008) Cediranib (AZD2171) is an active agent in recurrent epithelial ovarian cancer. *ASCO Proceedings* 26:2008, Abstract 5501.

Matulonis, U.A., S.T. Berlin, S.P. Ivy, *et al.* (2009) Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. *J Clin Onc*, in press.

McGuire, W.P., W.J. Hoskins, M.F. Brady, *et al.* (1996) Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *New Engl J Med* 334:1-6.

Nguewa, P.A., M.A. Fuertes, B. Valladares, *et al.* (2005). Poly(ADP-ribose) polymerases: homology, structural domains and functions. Novel therapeutic applications. *Progr Biophys Mol Bio* 88:143-172.

Ogilvie, D.J., J. Kendrew, S.T. Barry, *et al.* (2004) AZD2171, a high potent inhibitor of VEGF receptor signaling in primary human endothelial cells, exhibits broad-spectrum activity in tumor xenograft models. *Proc Am Assoc Cancer Res*: A4553.

Press, J.Z., A. DeLuca, N. Boyd, *et al.* (2008) Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. *BMC Cancer* 22(8): 17-24.

Pyrioichou, A., G. Olah, E.A. Deitch, *et al.* (2008) Inhibition of angiogenesis by the poly(ADP-ribose) polymerase inhibitor PJ-34. *Int J Mol Med* 22(1): 113-118.

Rustin, G. (2003) Use of CA125 to assess response to new agents in ovarian cancer trials. *J Clin Onc* 21(suppl 10): 187s-193s.

Sandhu, S.K., R.M. Wenham, G. Wilding, *et al.* (2010) First-in-human trial of a poly(ADP-ribose) polymerase (PARP) inhibitor MK-4827 in advanced cancer patients (pts) with antitumor activity in BRCA-deficient and sporadic ovarian cancers. *ASCO Proceedings* 28: 2010, Abstract 3001.

Shields, A.F., E. Heath, P. DeLuca, *et al.* (2007) AZD2171 in combination with various anticancer regimens: Follow-up results of a phase I multi-cohort study. *ASCO Proceedings* 25: 2007, Abstract 3544.

Sorlie, T., R. Tibshirani, J. Parker, *et al.* (2003) Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Nat Acad Sci* 100(14): 8418-8423.

Taniguchi, T., M. Tischkowitz, N. Ameziane, *et al.* (2003) Disruption of the Fanconi anemia-BRCA pathway in cisplatin-sensitive ovarian tumors. *Nat Med* 9(5): 568-574.

Tentori, L., P.M. Lacal, A. Muzi, *et al.* (2007) Poly(ADP-ribose) polymerase (PARP) inhibition or PARP-1 gene deletion reduces angiogenesis. *Eur J Cancer* 43(14): 2124-2133.

Virag, L., and C. Szabo. (2002) The therapeutic potential of poly(ADP-ribose) polymerase inhibitors. *Pharmacol Rev*: 54(3):375-429.

Wedge, S.R., D.J. Ogilvie, M. Dukes, *et al.* (2000) ZD1490: An orally active inhibitor of vascular endothelial growth factor signaling with broad-spectrum antitumor efficacy. *Cancer Res* 60:970-975.

Wedge, S.R., D.J. Ogilvie, M. Dukes, *et al.* (2002) ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis and tumor growth following oral administration. *Cancer Res* 62:4645-4655.

Yang, H.J., V.W. Liu, Y. Wang, *et al.* (2006) Differential DNA methylation profiles in gynecological cancers and correlation with clinico-pathological data. *BMC Cancer* 23(6): 212-220.

17. APPENDICES

APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	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.

DFCI IRB 09-293 APPENDIX B: PATIENT'S PILL DIARY: CEDIRANIB

Today's Date _____

Patient Name_____ Patient Study ID _____

Cycle #_____

(*initials acceptable for patient's name)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle (28 days).
2. You will take ___ (number) ____mg (dosage) tablet(s) each morning.
   You may take the tablet(s) one hour before or two hours after eating, as you prefer.
3. Record the date, the number of pills you took, and when you took them.
4. Please bring your pill bottle (including empty bottles) and this form to your physician when you go for your next appointment.

Date	Day	# pills and when taken: cediranib			Comments	Date	Day	# pills and when taken: cediranib			Comments
		15mg	20mg	Time				15mg	20mg	Time	
	1						15				
	2						16				
	3						17				
	4						18				
	5						19				
	6						20				
	7						21				
	8						22				
	9						23				
	10						24				
	11						25				
	12						26				
	13						27				
	14						28				

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____ Date patient was removed from study _____
2. Patient's planned daily dose_____ Total number of pills taken this month _____

Physician/Nurse/Data Manager's Signature

_____

DFCI IRB 09-293 APPENDIX B: PATIENT'S PILL DIARY: OLAPARIB (CAPSULE)

Today's Date _____

Patient Name_____ Patient Study ID _____

Cycle #_____

(*initials acceptable for patient's name)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle (28 days).
2. You will take ___ capsules each day twice a day 12 hours apart.
   You must take the capsules on an empty stomach either 1 hour before or 2 hours after meals.
3. Record the date, the number of capsules you took, and when you took them.
4. Please bring your pill bottle (including empty bottles) and this form to your physician when you go for your next appointment.

Date	Day	# capsules and when taken: olaparib # AM	# PM	Comments	Date	Day	# capsules and when taken: olaparib # AM	# PM	Comments
	1					15			
	2					16			
	3					17			
	4					18			
	5					19			
	6					20			
	7					21			
	8					22			
	9					23			
	10					24			
	11					25			
	12					26			
	13					27			
	14					28			

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____ Date patient was removed from study _____
2. Patient's planned daily dose_____ Total number of pills taken this month _____

Physician/Nurse/Data Manager's Signature

_____Date _____

DFCI IRB 09-293 APPENDIX B: PATIENT'S PILL DIARY: OLAPARIB (TABLET)

Today's Date _____

Patient Name_____ Patient Study ID _____

Cycle #_____

(*initials acceptable for patient's name)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle (28 days).
2. You will take __ (number) __mg (dosage) and ___ (number) ___mg (dosage) tablet(s) each day twice a day 12 hours apart. You must take the tablets on an empty stomach either 1 hour before or 2 hours after meals.
3. Record the date, the number of tablets you took, and when you took them.
4. Please bring your pill bottle (including empty bottles) and this form to your physician when you go for your next appointment.

Date	day	# tablets and when taken: olaparib								Comments	Date	day	# tablets and when taken: olaparib								Comments
		mg			AM	mg			PM				mg			AM	mg			PM	
		25	100	150	Time	25	100	150	Time				25	100	150	Time	25	100	150	Time	
	1											15									
	2											16									
	3											17									
	4											18									
	5											19									
	6											20									
	7											21									
	8											22									
	9											23									
	10											24									
	11											25									
	12											26									
	13											27									
	14											28									

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____ Date patient was removed from study _____
2. Patient's planned daily dose_____ Total number of tablets taken this month _____

Physician/Nurse/Data Manager's Signature

_____Date _____

DFCI IRB 09-293 APPENDIX B: PATIENT'S PILL DIARY: PK EXPANSION COHORT

Today's Date _____ Cycle # _____

Patient Name _____ Patient Study ID _____

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

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

OLAPARIB
Take _____ (number) _____ mg and _____ (number) _____ mg tablets twice a day 12 hours apart after a light meal.

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

Patient's Signature: _____ Date: _____

Physician/Nurse/Data Manager's Signature _____ Date_____

APPENDIX C: PATIENT'S BLOOD PRESSURE DIARY

Today's Date _____

Patient Name_____ Patient Study ID _____

INSTRUCTIONS TO THE PATIENT:

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

Date	AM readings	PM readings	Other readings (include time of day)	Date	AM readings	PM readings	Other readings (include time of day)
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

Date of this clinic visit:

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

APPENDIX D: List of Drugs that May Have Potential CYP3A4 Interactions

CYP3A4 Inducers (prohibited)

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

Note: Topical steroids are permitted. Please contact overall PI if systemic steroids are clinically indicated while on trial.

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

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

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

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

CYP3A4 Inhibitors

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

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

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

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

CYP3A4 Substrates (allowed – take note of possible interactions)

Alfentanil	Dexlansoprazole	Isradipine	Ranolazine
Alfuzosin	Dextromethorphan[2]	Itraconazole	Refabutin
Alprazolam	Diazepam	Ixabepilone	Repaglinide
Ambrisentan	Dihydroergotamine	Ketamine	Risperidone[2]
Amiodarone	Diltiazem	Ketoconazole	Ritonavir
Amlodipine	Disopyramide	Lansoprazole	Salmeterol
Aprepitant	Docetaxel	Lapatinib	Saquinavir
Aripiprazole	Domperidone[2]	Lercanidipine[2]	Sibutramine
Armodafinil	Doxorubicin	Levonorgestrel	Sildenafil
Astemizole[2]	Eletriptan	Lidocaine	Simvastatin
Atazanavir	Efavirenz	Lovastatin[2]	Sirolimus
Atorvastatin	Eplerenone	Lopinavir	Solifenacin
Benzphetamine	Ergoloid mesylates	Maraviroc	Spiramycin
Bisoprolol	Ergonovine	Medroxyprogesterone	Sufentanil
Bortezomib	Ergotamine	Mefloquine	Sunitinib
Bosentan	Erlotinib	Mestranol	Tacrolimus
Bromazepam	Erythromycin	Methadone	Tadalafil
Bromocriptine	Escitalopram	Methylergonovine	Tamoxifen
Budesonide	Esomeprazole	Methyloprednisolone	Tamsulosin
Buprenorphine	Estradiol	Miconazole	Temsirolimus
Buspirone	Estrogens, conjugated	Midazolam	Telithromycin
Busulfan	synthetic	Mirtazapine	Teniposide
Cafergot[2]	Estrogens, conjugated	Modafenil	Terfenadine[2]
Caffeine[2]	equine	Montelukast	Testosterone[2]
Carbamazepine	Estrogens, esterified	Nateglinide	Tetracycline
Cerivastatin[2]	Estropipate	Nefazodone	Theophylline
Chlordiazepoxide	Eszopiclone	Nelfinavir	Tiagabine
Chloroquine	Ethinyl estradiol	Nevirapine	Ticlopidine
Chlorpheniramine	Ethosuximide	Nicardipine	Tinidazole
Ciclesonide	Etoposide	Nifedipine	Tipranavir
Cilostazol	Exemestane	Nilotinib	Tolterodine
Cisapride	Felbamate	Nimodipine	Toremifene
Citalopram	Felodipine	Nitrendipine[2]	Tramadol
Clarithromycin	Fentanyl	Nisoldipine	Trazodone
Clobazam	Finasteride[2]	Norethindrone	Triazolam
Clonazepam	Flunisolide	Norgestrel	Trimethoprim
Clorazepate	Flurazepam	Omeprazole	Trimipramine
Cocaine	Flutamide	Ondansetron	Vardenafil
Codeine[2]	Fluticasone	Paclitaxel	Venlafaxine
Colchicine	Fosamprenavir	Paricalcitol	Verapamil
Conivaptan	Fosaprepitant	Pazopanib	Vinblastine
Cyclophosphamide	Gefitinib	Pimozide	Vincristine
Cyclosporine	Haloperidol	Primaquine	Vinorelbine
Dantrolene	Hydrocortisone[2]	Propranolol[2]	Zaleplon[2]
Dapsone	Ifosfamide	Progesterone	Ziprasidone[2]
Darifenacin	Imatinib	Quazepam	Zolpidem
Darunavir	Indinavir	Quetiapine	Zonisamide
Dasatinib	Irinotecan	Quinidine	Zopiclone
Delavirdine	Isosorbide dinitrate	Quinine	
Dexamethasone	Isosorbide mononitrate	Rabeprazole	

* Note: CYP3A4 Substrate Table adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Drug Information Handbook 20th ed. Hudson, OH; LexiComp Inc. 2011-2012: 1810-1818

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

APPENDIX E: 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 F: Medications that May Cause QTc Prolongation

This table lists drugs that may prolong the QT_c interval. Cediranib may be administered after a 5 half-life washout period elapses following discontinuation of prohibited drugs. Drugs labeled "Use discretion" may be co-administered in the absence of other risk factors and with appropriate monitoring. Drugs with a weak association may be administered at usual doses with appropriate monitoring.

Compound	Compound Half Life	QTc Prolongation Association/ Concurrent Administration	Possible Washout Period – Hours	Possible Washout Period - Days
Alfuzocin	~10 hours	Some/Use Discretion		7
Amantadine	17 +/- 4 hours (10-25)	Some/Use Discretion		4
Amiodarone (cordarone)	**58 days (15-142) 36 days (active metabolite)**	**Strong/Prohibited**		**180**
Amitriptyline*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Amoxapine	~ 8 hours	Weak/At usual doses	40 hours	2 days
Ampicillin	1 to 1.5 hours	Weak/At usual doses		
Arsenic trioxide	**Not characterized; may be weeks**	**Strong/Prohibited**		
Azithromycin	40 hours	Some/Use Discretion		
Bepridil	**42 hr (26-64)**	**Strong/Prohibited**		**10**
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $T_{1/2}$=7-10 hour)	Some/Use Discretion	48	
Chloroquine	**6 to 60 days; mean 20 days**	**Strong/Prohibited**		
Chlorpromazine	**30 +/- 7 hours**	**Strong/Prohibited**		**7**
Ciprofloxacin	3.5 to 4.5 hours	Weak/At usual doses		
Cisapride	**6 – 12 hour, up to 20 hour**	**Strong/Prohibited**	**60**	
Citalopram		Weak/At usual doses		
Clarithromycin	**Non linear PK3-4 hr**	**Strong/Prohibited**	**36**	**3**

	(250mg Q12) **5-7 hr (500mg Q12)**			
Clomipramine	~ 21 hours	Weak/At usual doses		
Clozapine	12 hours at steady state	Some/Use Discretion		
Desipramine*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Disopyramide	**6.7 hr (4-10)**	**Strong/Prohibited**	**36**	
Dofetilide	**10 hr**	**Strong/Prohibited**	**48**	
Dolesetron	8.1 hr	Some/Use Discretion		
Domperidone	**7-8 hr**	**Strong/Prohibited**	**48**	
Doxepin*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Droperidol	**2.2 hours**	**Strong/Prohibited**	**10**	
Erythromycin	*** Each salt form has different Half life***	**Strong/Prohibited**		
Felbamate	20-23 hr	Some/Use Discretion		5
Flecainide	20 hr (12-27)	Some/Use Discretion		5
Fluconazole	~ 30 hours	Weak/At usual doses		
Foscarnet	87.5+/-41.8 hours *distribution and release from bone*	Some/Use Discretion		20
Fosphenytoin	12-29 hr	Some/Use Discretion		6
Galantamine		Weak/At usual doses		
Gatifloxacin	7-14 hr	Some/Use Discretion	48	
Gemifloxacin	7 hours	Some/Use Discretion	48	
Granisetron	3 to 4 hours	Some/Use Discretion		
Grepafloxacin	16 hr	Some/Use Discretion		3
Halofantrine	**6-10 days (variable among individual)**	**Strong/Prohibited**		**45**
Haloperidol	**18 +/-5 hr**	**Strong/Prohibited**		**5**
Ibutilide	**6 hours (2-12) * variable among subject***	**Strong/Prohibited**	**36**	**3**
Imipramine*	> 24 hours, wide	Weak/At usual		

	interpatient variability	doses		
Indapamide	14 hours (biphasic elimination)	Some/Use Discretion		3
Isradipine	8 hours (multiple metabolites)	Some/Use Discretion	48	
Itraconazole	20 hours, increasing to 40 hours	Weak/At usual doses		
Ketoconazole	2 hours, increasing to 8 hours	Weak/At usual doses		
Levofloxacin	6-8 hours	Some/Use Discretion	48	
Levomethadyl	**Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM**	**Strong/Prohibited**		**20**
Lithium	24 hour (10-50)	Some/Use Discretion		7
Mefloquine	13 to 24 days	Weak/At usual doses		
Mesoridazine	**24-48 hours (animal study)**	**Strong/Prohibited**		**10**
Methadone	**15-30 hours**	**Strong/Prohibited**		**7**
Mexiletine	>10 hours	Weak/At usual doses		
Moexipril/HCTZ	2-9 hour (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	Some/Use Discretion	48	
Moxifloxacin	12 +/-1.3 hours	Some/Use Discretion	72	
Naratriptan	6 hours		36	
Nicardipine	~ 2 hour post IV infusion	Some/Use Discretion	12	
Nortriptyline*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Octreotide	1.7 hours	Some/Use Discretion	12	
Ofloxacin	5 to 7.5 hours	Some/Use Discretion		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)	Some/Use Discretion		1 to 3
Paroxetine		Weak/At usual doses		
Pentamidine	**6.4+/-1.3 hours**	**Strong/Prohibited**	**36**	
Pimozide	**55 hours**	**Strong/Prohibited**		**10**

Procainamide	**3-4 hour for PA and NAPA (active metabolite)**	**Strong/Prohibited**	**24**	**3**
Protiptyline*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Quetiapine	6 hours	Some/Use Discretion	36	
Quinidine	**6-8 hours in adult; 3-4 hours in children**	**Strong/Prohibited**	**36**	
Quinine	4-5 hours	Weak/At usual doses		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T ½ =21-30 hours (extensive to poor metabolizer)	Some/Use Discretion		4
Roxithromycin		Some/Use Discretion		
Salmeterol	5.5 hours (only one datum)	Some/Use Discretion	36	
Sertraline	~ 26 hours	Weak/At usual doses		
Solifenacin	40 to 68 hours	Weak/At usual doses		
Sotalol	**12 hours**	**Strong/Prohibited**	**72**	
Sparfloxacin	**20 hours (16-30)**	**Strong/Prohibited**		**4**
Sumatriptan	2.5 hours		12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant	Some/Use Discretion		7
Tamoxifen	5-7 days (biphasic)	Some/Use Discretion		30
Telithromycin	2-3 hr	Some/Use Discretion	24	
Thioridazine	**20-40 hours (Phenothiazines)**	**Strong/Prohibited**		**7**
Tizanidine	2.5 hours	Some/Use Discretion	12	
Trimethoprim/sulfa	6 to 17 hours	Weak/At usual doses		
Trimipramine	~ 23 hours	Weak/At usual doses		
Vardenifil	4 to 5 hours	Some/Use Discretion		

Venlaflaxine	5 +/-2 hours for parent comp. 11+-2 hours for OVD (active metabolite)	Some/Use Discretion	60	
Voriconizole	6 hours; dose dependent	Some/Use Discretion		
Ziprasidone	7 hr	Some/Use Discretion	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	Weak/At usual doses	18	

*** These agents are tricyclic antidepressants; traditionally, they have only been associated with QTc interval prolongation at serum levels approaching or into the range of toxicity. Special caution is advised is the elderly and children/adolescents.**

References:

1. Physician's Desk Reference 2002
2. Facts and Comparisons (update to June 2005)
3. The Pharmacological Basis of Therapeutics 9th Edition, 1996
4. ArizonaCERT Center for Education and Research on Therapeutics, https://www.crediblemeds.org/index.php

Disclaimer: This chart was updated on August 23, 2005. It may not include all drugs associated with QTc prolongation. Prescribers are advised to do further research if they have additional questions.

DFCI IRB Protocol # 09-293

APPENDIX G:

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

Table of Contents

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations (21 CFR Part 11); Good Clinical Practice (GCP) Guidelines; and Health Insurance Portability and Accountability Act (HIPAA) requirements in accordance with the CTEP Multi-center Guidelines.

1.2 Multi-Center Data and Safety Monitoring Plan Components

The Multi-Center Data and Safety Monitoring Plan includes the following components:

DF/HCC Multi-center Protocol: One or more outside institutions collaborating with Dana-Farber/Harvard Cancer Center on a research protocol where DF/HCC is the Lead Institution. Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates are not viewed as outside sites in this definition.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center sites (DFCI, MGH, BIDMC, CH, BWH) will be the Lead Institution and will be responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, FDA, OBA etc.).

DF/HCC Contract Principal Investigator: Investigator located at the Lead Institution who will be charged with the responsibility of the administration of the DF/HCC Project. This most often will be the Protocol Chair, but occasionally this may be the overall grant or contract holder, as applicable.

Protocol Chair: The Protocol Chair is the Principal Investigator for the DF/HCC protocol submitted as the Lead Institution. For applicable protocols, the Protocol Chair will be the single liaison with any regulatory agencies (i.e. CTEP Protocol and Information Office (PIO), FDA, OBA etc.).

Participating Institution: A participating institution is an institution that desires to collaborate with DF/HCC and commits to accruing participants to a DF/HCC protocol. The participating institution acknowledges the Protocol Chair as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The Lead Institution is the Coordinating Center for the DF/HCC Multi-center Protocol. The Coordinating Center will provide the administrative support to the Protocol Chair in order that he/she may fulfill the responsibilities outlined in the DSMP and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In addition to the Lead Institution, the Quality Assurance Office for Clinical Trials (QACT) provides support services to

assist the Protocol Chair.

2. GENERAL ROLES AND RESPONSIBILITIES

In accordance with the CTEP Multi-center Guidelines, the Protocol Chair (DF/HCC Principal Investigator), Coordinating Center (Lead Institution or designee), and the Participating Institutions will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the DSMP):

2.1 Protocol Chair (DF/HCC Principal Investigator)

The Protocol Chair, **Joyce Liu**, will accept responsibility for all aspects of the Multi-Center Data and Safety Monitoring Plan to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Submit the Multi-Center Data and Safety Monitoring Plan as an inclusion to the protocol.
- Assure all participating institutions are using the correct version of the protocol.
- Monitor progress and overall conduct of the study at all participating institutions.
- Ensure all DFCI IRB, DF/HCC and other applicable (i.e. CTEP) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with CTEP/PIO Office (CTEP trials).
- Identify participating institutions and obtain accrual commitments. The title page must include the names and contact information for all participating institutions that perform the function of recruiting, enrolling, and treating participants for the protocol. The Coordinating Center (Lead Institution or designee) must be designated on the title page.

2.2 Coordinating Center (Lead Institution)

The Coordinating Center is the DF/HCC Lead Institution's study team or designee (i.e Medical Monitor, Clinical Research Organization). The DF/HCC Lead Institution **Dana-Farber Cancer Institute** will ensure that all participating sites within the Multi-Center Protocol demonstrate their intent and capability of complying with Federal Regulations, GCPs and Health Insurance Portability and Accountability Act (HIPAA) requirements. To assist the Protocol Chair in meeting his/her responsibilities as required by the DSMP, the DF/HCC Lead Institution's study team or designee will assume the following general responsibilities:

- Assist in protocol review.
- Maintain copies of Institutional Review Board (IRB) approvals from all participating institutions.
- Maintain CTEP correspondence.
- Maintain updated roster of participants.
- Verify eligibility.

- Verify response.
- Collect data on protocol specific CRFs.
- Prepare all submitted data for review by the Protocol Chair.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to Protocol Chair for timely review.
- Distribute external Serious Adverse Event safety reports.
- Monitor and audit Participating Institutions either by on-site inspection of selected participant records and/or with source documents and research records submitted to the Lead Institution.

In addition to the Lead Institution, the DF/HCC Quality Assurance Office for Clinical Trials provides the following support services to assist the Protocol Chair:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide Central Participant Registration.
- Confirm eligibility and consent.
- Provide auditing services (funding and QACT approval required).

2.3 Participating Institutions

The Participating Institutions will be identified on the title page for each protocol. In addition, each participating institution will provide to the Lead Institution or designee a list of the key personnel assigned to the role for oversight of data management at their site. All sites must have office space, office equipment, and internet access that meet HIPAA standards.

The general responsibilities for each participating institution are as follows:

- Commit to accrual to the Lead Institution's (DF/HCC) protocol.
- Submit protocol and/or amendments to their local IRB.
- Update Coordinating Center (Lead Institution or designee) with research staff changes on a timely basis.
- Register participants through the QACT.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center (Lead Institution or designee).
- Submit Serious Adverse Event reports to local IRB and directly to the Coordinating Center (Lead Institution or designee). For CTEP trials, submit SAE reports directly to CTEP and provide copies to the Coordinating Center (Lead Institution or designee).
- Submit deviations and violations to local IRB and the Coordinating Center (Lead Institution or designee).
- For protocols using investigational agents, the participating institution will order their own investigational agents regardless of the supplier (i.e. NCI, pharmaceutical company).

3. DF/HCC QUALITY ASSURANCE OFFICE FOR CLINICAL TRIALS

The DF/HCC QACT is a unit that has been developed to computerize, manage, and monitor data for DF/HCC trials. The DF/HCC QACT is located administratively in the office of the Senior Vice President for Clinical Research, at Dana-Farber Cancer Institute. The QACT uses DF/HCC computerized institutional databases for participant registrations and for the management of trial data as well as a set of quality assurance programs designed to monitor DF/HCC trials.

3.1 Organizational Structure

The DF/HCC Quality Assurance Office for Clinical Trials administrative structure consists of:

DF/HCC Quality Assurance Officer for Clinical Trials: Oversees the functions of the DF/HCC QACT.

QACT Assistant Director for Data: Provides direct oversight to the QACT Data Analysts assigned to CRF design, data collection and computerization for DF/HCC trials.

The DF/HCC QACT Data Analysts will be assigned on a protocol by protocol basis. Each protocol's data analyst is responsible for database management, data entry, data quality assurance, and protocol specific correspondence related to the collection and quality assurance of data.

QACT Assistant Director for Monitoring: Provides direct oversight to the QACT Protocol Registrars and Clinical Research Auditors.

The DF/HCC Protocol Registrars are responsible for the confirmation of each participant's eligibility and consent prior to protocol registration.

If funded and QACT approved, the DF/HCC Clinical Research Auditors may assist the Lead Institution in their auditing responsibilities for multi-center trials. The QACT auditor is responsible for systematically evaluating participant safety, protocol compliance, institutional SOPs, ICH GCP and Federal regulation compliance, data accuracy and investigational drug handling to assure a high standard of quality for DF/HCC trials.

4. PROTOCOL DEVELOPMENT

4.1 Activation of a Protocol

The Protocol Chair is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting SAEs, violations and deviations per DFCI IRB guidelines and CTEP Multi-center Guidelines. Further, the Protocol Chair will be the single liaison with the CTEP/PIO.

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

- Inclusion of the DF/HCC Multi-Center Data and Safety Monitoring Plan in the protocol as an appendix.
- Identify participating institutions and obtain accrual commitments. The title page must include the names and contact information for all participating institutions that perform the function of recruiting, enrolling, and treating participants for the protocol. The Coordinating Center (Lead Institution or designee) must be designated on the title page.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the Protocol and that all Participating Institutions use the correct version.
- Oversee the development of data collection forms (case report forms) that are of common format for use at all the Participating Institutions.

4.2 Coordinating Center Support Function

The DF/HCC Lead Institution's study staff or designee will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the DF/HCC Lead Institution's study staff or designee include:

- Review of the protocol and consent to check for logistics, spelling, and consistency. Provide the Protocol Chair a list of queries related to any inconsistencies.
- Provide necessary administrative sections, including paragraphs related to registration logistics, data management schedules, and multi-center guidelines.
- Maintenance of contact list of all participating institutions in the DF/HCC Multi-center Protocol and the distribution of updates to the sites as needed.
- Derivation of the study calendar, if applicable.
- Assistance in preparation and maintenance of case report forms. Conduct regular communications with all participating sites (conference call, emails, etc). Maintain documentation of all communications.

5. PROTOCOL MANAGEMENT

The Coordinating Center (Lead Institution of designee) is responsible for assuring that each Participating Institution in the DF/HCC Multi-center Protocol has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the Lead Institution or designee must maintain copies of all IRB approvals, for each participating institution.

5.1 Protocol Distribution

The Coordinating Center (Lead Institution or designee) will distribute the final approved protocol and any subsequent amended protocols to all Participating Institutions.

5.2 Protocol Revisions and Closures

The participating institutions will receive phone, fax, mail or e-mail notification of protocol revisions from the Lead Institution or designee. It is the individual participating institution's responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating institutions will receive written notification of protocol revisions regarding non life-threatening events from the Lead Institution or designee. Non-life-threatening protocol revisions should be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening Causes: Participating institutions will receive telephone notification from the Lead Institution or designee concerning protocol revisions required to protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval

Protocol Closures and Temporary Holds: Participating institutions will receive fax, e-mail, or phone notification of protocol closures and temporary holds, with follow-up by mail from the Lead Institution or designee. Closures and holds will be effective immediately. In addition, the Lead Institution or designee will update the Participating institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

5.3 Informed Consent Requirements

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is DF/HCC policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials.

5.4 IRB Documentation

The following must be on file with the DF/HCC Lead Institution or designee prior to participant registration:

- Approval Letter of the institution's IRB (An Expedited IRB first approval is NOT acceptable)
- IRB approval for all amendments

It is the individual institution's responsibility to notify its IRB of protocol revisions. Participating institutions will have 90 days from receipt to provide the DF/HCC Lead Institution or designee their IRB approval for Major Amendments to a protocol.

DF/HCC defines a Major Amendment as: A substantive change in the study which may increase or decrease the risk to study participants. Major revisions require full IRB approval. The following criteria are examples of revisions to a protocol that are considered to be major amendments:

- Change of eligibility (inclusion/exclusion) criteria
- Change in design of protocol
- Change in statistical section
- Change in sample size/accrual (e.g., doubling the sample size)
- Change in informed consent
- Change of estimated dropout rate
- Change of treatment or intervention
- Change of device
- Change in primary objective evaluation process

5.5 IRB Re-Approval

Annual IRB re-approval from the Participating institution is required in order to register participants onto a protocol. There is no grace period for annual re-approvals.

Protocol registrations will not be completed if a re-approval letter is not received by the DF/HCC Lead Institution or designee from the Participating Institutions on or before the anniversary of the previous approval date.

5.6 Participant Confidentiality and Authorization Statement

The Health Insurance Portability and Accountability Act of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or disclosed in the course of treatment, payment or health care operations. The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which has modified the privacy rule in significant ways vis-à-vis research.

In order for covered entities to use or disclose protected health information during the course of a DF/HCC Multi-Center Protocol the study participant must sign an Authorization. This Authorization may or may not be separate from the Informed Consent. The DF/HCC Multi-Center Protocol, with the approval from the DFCI IRB and NCI/CTEP, will provide an Informed Consent template, which covered entities (DF/HCC Multi-Center Protocol participating institutions) must use.

The DF/HCC Multi-Center Protocol will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per National Cancer Institute requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

5.7 Participant Registration and Randomization

To register a participant, the following documents should be completed by the DF/HCC Multi-Center Protocol participating site and faxed to or e-mailed to the Lead Institution or designee (Contact Information: Emily Eisenberg; email: emily_eisenberg@dfci.harvard.edu; phone: (617) 632-6930; fax: (617) 632-3550):

- Copy of required laboratory tests:
  - CBC with differential
  - Serum chemistries (Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, phosphorus, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, LDH)
  - Troponin T or I, TSH and Free T4
  - Urinalysis or urine protein:creatinine ratio
  - CA-125
- Signed informed consent form
- HIPAA authorization form (if separate from the informed consent document)
- Completed and Signed QACT Eligibility Screening Worksheets
- CT Scan
- Pathology report
- Most recent clinic visit note

The research DF/HCC Multi-center Protocol participating site will then call or e-mail the Lead Institution or designee to verify eligibility. To complete the registration process, the Lead Institution or designee will:

- Register the participant on the study with the DF/HCC Quality Assurance Office for Clinical Trials (QACT)
- Fax or e-mail the participant case number, and if applicable the dose treatment level, to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration

Randomization can only be done between normal QACT business hours, 8:30am-5:00pm.

5.8 DF/HCC Multi-center Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT CRF/eCRF completion and written on all data and QACT correspondence for the participant.

5.9 DF/HCC Multi-center Protocol Registration Policy

5.9.1 Initiation of Therapy: Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the site receives a faxed or e-

mailed copy of the participant's Registration Confirmation memo from the DF/HCC QACT. Therapy must be initiated per protocol guidelines. The Protocol Chair and DFCI IRB must be notified of any exceptions to this policy**.**

5.9.2 Eligibility Exceptions: The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. In addition, the Cancer Therapy Evaluation Program (CTEP) specifically prohibits registration of a participant on any NCI Sponsored protocol that does not fully and completely meet all eligibility requirements. The DF/HCC QACT requires each institution to fully comply with this requirement.

5.9.3 Verification of Registration, Dose Levels, and Arm Designation: A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one working day of the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

5.9.4 Confidentiality: All documents, investigative reports, or information relating to the participant are strictly confidential. Any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Lead Institution or designee must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number and protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification.

5.10 Schedule of Data Submission

The DF/HCC QACT develops a set of either paper or electronic case report forms, (CRF/eCRFs) for use with the DF/HCC Multi-Center Protocol. QACT provides a web based training for eCRF users. These forms are designed to collect data for each study. The schedule for submission of case report forms to the DF/HCC QACT is generally specified in each protocol. When not specified in the protocol, the DF/HCC QACT will require the forms to be submitted as follows:

Note: It is necessary to send only ONE copy of all paper Case Report Forms, if applicable.

5.10.1 Eligibility Checklist

Purpose - Outlines protocol-specific eligibility criteria and includes the following:

Participant Demographics (address, zip code, sex, race, ethnicity, initials, date of birth)
1) Parameters for eligibility
2) Parameters for exclusion
3) Parameters for stratifications

If a time frame is not specified in the protocol, tests must be completed as follows:

- Lab tests required for eligibility must be completed within 14 days prior to study enrollment by the QACT.
- For protocols requiring measurable disease, lab baseline measurements must be completed within 14 days prior to study enrollment by the QACT. A baseline CA-125 must be drawn within 7 days of starting treatment.
- Tumor measurements by MRI or CT must be completed within 28 days of initiating treatment. Other non-lab tests required for eligibility must be performed within 30 days prior to study entry.

Schedule for Submission - Completed prior to participant registration. The Informed Consent/ Participant Authorization for the Release of Personal Health Information should be submitted with the Eligibility Checklist at the time of registration.

5.10.2 On-study Form

Purpose - documents the following items:
- Demographic data
- Prior therapy
- Past medical and surgical history
- Description of participant's physical status at protocol registration
- Disease site specific data

Schedule for Submission - Submitted to DF/HCC QACT within 14 days after registration.

5.10.3 Baseline Assessment Form

Purpose – Documents objective and subjective disease status as defined by the protocol**.** Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

Schedule of Submission – Submitted within 14 days after registration.

5.10.4 Treatment Form

Purpose - Records the following information related to the time the participant receives protocol treatment:
- Participant, Protocol, Affiliate information
- Protocol treatment and supportive therapy per treatment cycle
- Protocol specific laboratory values per treatment cycle
- All medications other than protocol chemotherapy agents used to treat concomitant diagnoses, if applicable

Schedule for Submission – Submitted within 10 days after the last day of the cycle.

5.10.5 Adverse Event Report Form

Purpose – Documents adverse events that occur while the participant is receiving treatment and for up to 30 days after the last dose of treatment. All adverse events are to be graded by number using the toxicity grading scale required by the protocol. This form is not for IRB submission, but for recording the AE in the research database.

Schedule for Submission – Submitted within 10 days after the last day of the cycle.

5.10.6 Response Assessment Form

Purpose – Documents objective and subjective response as defined by the protocol. Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

Schedule of Submission – Submitted within 10 days after the completion of the cycle required for response evaluation.

5.10.7 Off Treatment/Off Study Form

Purpose - The Off Treatment/Off Study Form is submitted when the participant is removed from the study or has completed all protocol treatment. Note: If the participant dies while on protocol, the Off Study Form is the last form submitted.

Schedule of Submission – Submitted within 14 days after completing treatment or taken off study for any reason.

5.10.8 Follow up / Survival Form

Purpose - Summarizes participant status at a given point in time after being removed from treatment.

Schedule of Submission – Submitted within 14 days after the protocol defined follow up visit date or call.

5.11 Data Form Review

When data forms arrive at the DF/HCC QACT, they are reviewed for:

Timelines:
Did the form arrive on time as specified in the protocol?

Completeness:
Is all the information provided as required per protocol?

Participant Eligibility:

Does the participant meet the eligibility requirements for the study based on the demographic data, lab values and measurements provided?

Stratification:
Are the stratification parameters consistent with what was given at the time of registration?

Protocol Treatment Compliance:
Are the body surface area (BSA) and drug dosage calculations correct? The dose must be within 10% of the calculated protocol dose.

Adverse Events (Toxicities):
Did the participant experience adverse events (toxicities or side effects) associated with the treatment? Was the treatment delayed due to the adverse event? What was the most severe degree of toxicity experienced by the participant?

Notations concerning adverse events will address relationship to protocol treatment for each adverse event grade. All adverse events encountered during the study will be evaluated according to the NCI Common Toxicity Criteria assigned to the protocol and all adverse events must be noted on the participant's Adverse Event (Toxicity) Forms.

Response:
Did the participant achieve a response? What level of response did they achieve? On what date did the participant achieve the response and how was the response determined?

Response criteria are defined in the protocol. A tumor assessment must be performed prior to the start of treatment and while the participant is on treatment as specified by the protocol.

Objective responses must have documentation such as physical measurements, x-rays, scans, or laboratory tests.

A subjective response is one that is perceived by the participant, such as reduction in pain, or improved appetite.

5.12 Missing and Deficient Memorandum

Data submissions are monitored for timeliness and completeness of submission. Participating institutions are notified of their data submission delinquencies in accordance with the following policies and procedures:

<u>Incomplete or Questionable Data</u>

If study forms are received with missing or questionable data, the submitting institution will receive a written query from the DF/HCC QACT Data Analyst. Responses to the query should

be completed and returned within 14 days. Responses may be returned on the written query or on an amended case report form. In both instances the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the participating institution will receive a Missing Form Report from the DF/HCC QACT noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of three times a year.

6. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol.

Participating sites should order their own agent.

The agents in the study are investigational, and the pharmacy must be able to receive and store the agent. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

6.1 CTEP Trial Routine Drug Requisitions

Investigational drugs for use in Cancer Therapy Evaluation Program's (CTEP) approved protocols are obtained through the Pharmaceutical Management Branch at CTEP in accordance with the guidelines provided in the NCI's Investigator Handbook. The DF/HCC Multi-center Protocol institutions may order drugs directly from Division of Cancer Treatment and Diagnosis (DCTD) through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx>.

6.1.1 Guidelines for Clinical Drug Request Submission:

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 < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Orders will only be shipped to the investigator's designated shipping address. All changes to the investigator's shipping address must be in writing and signed by the investigator/designee.

1) Orders must use the NCI protocol numbers only.
2) Limit drug requests to an eight week supply.

3) When a number of investigators are participating on a clinical study at the same institution, one investigator should be considered or designated the principal investigator under whom all investigational agents for that protocol should be ordered.

Normal PMB processing time will be two (2) working days. Orders will be shipped within two working days based on drug availability and provided there are no shipping restrictions, (e.g. thermo-labile agents, holiday restrictions).

Requests for next day delivery must be received at PMB by 2:30 PM, Eastern Time. Next day delivery must be stated on the order and an express courier account number must be provided. If there are any comments or suggestions, direct them to the PMB by phone (240) 276-6575 or PMBafterhours@mail.nih.gov.

6.2 Medical Emergency Drug Ordering

Clinical drug requests are submitted through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. The need-by date should be specified accordingly and an overnight courier number provided if the shipment is needed urgently.
All orders sent via overnight courier are filled the same day if the order arrives before 2:30 PM, EST.

7. SAFETY ASSESSMENTS AND TOXICITY MONITORING

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria assigned to the protocol and recorded prior to each course of therapy. This study will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Life-threatening toxicities should be reported immediately to the Protocol Chair and Institutional Review Board (IRB). Protocols using CTEP supplied agents should also report these toxicities via the CTEP-AERS system.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

7.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse drug experience at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions in a participant who has never had seizure activity in the past that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

Unless otherwise specified in the protocol, the study will utilize the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 for Toxicity and Adverse Event reporting until March 31, 2018. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.2 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Serious Adverse Events (SAEs) will be followed as is delineated in the protocol Section 11.

Participating Institutions must report serious adverse events for CTEP trials online using CTEP-AERS. This applies to any medical event equivalent to an unexpected grade 2 with a possible, probable or definite attribution, most grade 3 and all grade 4 and grade 5 (death) toxicities regardless of study phase or attribution.

In addition, the Participating Institutions must report the serious adverse events to the Protocol Chair and the Coordinating Center (Lead Institution) following the DFCI IRB SAE Reporting Requirements.

The Lead Institution will maintain documentation of all Adverse Event Reporting and be responsible for communicating all SAEs that are related to study drug(s) to all Participating sites.

7.3 Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. In compliance with these FDA regulations, the Protocol Chair is responsible for reviewing all IND Safety Reports and forwarding the IND Safety Reports to the Participating Institutions. The investigator's are to file a copy with their protocol file and send a copy to their IRB according to their local IRB's policies and procedures.

CTEP will notify the Participating sites via the DF/HCC Lead Institution by the following methods: Investigators will be sent a copy of expedited adverse events which CTEP has sent to the FDA. CTEP will notify the Protocol Chair at the Lead Institution. Within 7 business days of receipt of the notification, the Lead Institution or designee will forward the letters to the Participating sites with protocol specific instructions for IRB submissions, participant notifications, etc. For routine IND Safety Reports, CTEP does not generally require an immediate revision to the protocol and/or model informed consent documents. The investigators are to file a copy with their protocol file and send a copy to their IRB according to their local IRB's policies and procedures.

8. PROTOCOL VIOLATIONS AND DEVIATIONS

Neither the FDA nor the ICH GCP guidelines define the terms "protocol violation" or "protocol deviation." All DF/HCC Protocol Chairs must adhere to those policies set by the DFCI IRB, the definitions for protocol violation and deviation as described by the DFCI IRB will be applied for reporting purposes for all institutions participating in the DF/HCC Multi-center Protocol.

8.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g., enrollment of a subject who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

8.2 Reporting Procedures

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record to describe all protocol exceptions, deviations and violations.
The Protocol Chair will **also** be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from DFCI IRB. The Participating institution must submit the deviation request to the Protocol Chair or designee, who will submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation should be submitted to the participating site's own IRB, per its institutional policy.

A copy of the participating institution's IRB report and determination will be forwarded to the DF/HCC Lead Institution or designee by mail, facsimile, or via e-mail within 10 business days after the original submission.

All protocol violations must be sent to the DF/HCC Lead Institution Protocol Chair or designee in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the participating institution, the DF/HCC Lead Institution or designee will submit the report to the Protocol Chair for review. Subsequently, the participating institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

9. QUALITY ASSURANCE

The quality assurance process for a clinical trial research study requires verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution or designee with the aid of the QACT provides quality assurance oversight for the DF/HCC Multi-center Protocol.

9.1 Ongoing Monitoring of Protocol Compliance

All data submitted to the DF/HCC QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion. The Lead Institution or designee and if applicable QACT Data Analysts assigned to the Protocol will perform the ongoing protocol compliance monitoring with the support of the participating institution's Coordinators, the Principal Investigators, and the Protocol Chair.

Participating institutions will be required to submit source documents for monitoring to the Coordinating Center, Clinical Research Specialist, and/or QACT as requested for ongoing virtual monitoring. On-site and/or virtual monitoring will be conducted by the Clinical Research Specialist at all participating institutions. Monitoring activities will include, but are not limited to, review of the following: source documentation supporting data submitted, eligibility requirements of all participants, informed consent documents, adverse events and all associated documentation, records of study drug storage/administration/treatment, regulatory records and site Trial Master File, protocol deviations/violations, and response assessments. The Lead Institute will conduct an on-site monitoring visit after three patients have been accrued at a site, or at a minimum once a year for sites with active patients. Additional on-site monitoring visits will be scheduled if there are significant findings or discrepancies to be resolved. An on-site SIV will be conducted at each site prior to study activation, and a study manual outlining specific study instructions will be given to each site. Additionally, QACT and/or the Clinical Research Specialist will periodically review data for completion and quality of information submitted, and the sites' overall adherence to protocol requirements, regulatory compliance, good clinical practice, and accrual goals.

The Coordinating Center will provide regular communication to participating sites via email and biweekly teleconference updates, SAE reporting, amendment submissions, and other regulatory activities. The Coordinating Center will be available to all sites' study team members for

resolving questions, concerns and facilitating compliance. It is the primary responsibility of the Principal Investigator and Clinical Research Specialist to ensure that sites maintain accurate and completed documentation and CRF submission to DF/HCC

9.2 Evaluation of Participating Institution Performance

9.2.1 Eligibility Checklist: Eligibility criteria are checked on a protocol-specific eligibility checklist and faxed to the DF/HCC QACT prior to registration on protocol. The checklist and informed consent document are reviewed by a DF/HCC QACT Protocol Registrar before the participant can be registered on a protocol. The DF/HCC QACT cannot make exceptions to the eligibility requirements.

9.2.2 Accrual of Eligible Participants: Annual accrual rates for eligible participants enrolled onto therapeutic clinical trials is calculated for each institution. Institutions are expected to maintain the minimum annual average accrual as defined by the protocol grant or contract.

9.2.3 Quality Improvement Report: For CTEP trials, the DF/HCC Lead Institution is bound by institutional and federal regulations in the conduct of cancer research trials; protocol performance is reported to the NCI annually.

Yearly quality improvement reports will summarize proficiency from January 1 – December 31 and will be sent to the NCI in January.

The DF/HCC Lead Institution will distribute Quality Improvement Reports (QI) to each institution on a semi-annual basis to help the affiliate monitor data management and detect changes over time. This data can be used to detect trends in protocol adherence and present opportunities for improvement. The semi-annual reporting period will be:

January 1 - June 31
July 1 - December 31

9.3 On-Site Auditing

Auditing is a method of Quality Assurance. The main focus in auditing is to measure if the standards and procedures set are being followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and the data were generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the Code of Federal Regulations.

9.3.1 DF/HCC Sponsored Trials

Auditing visits will occur as needed and at least once for all enrolling sites. Auditing will be performed by the DF/HCC QACT. Auditing visits entail source verification and review of the

following: study drug administration/treatment, informed consent procedures, pharmacy records, study drug, eligibility criteria, adverse events, response assessments, procedures and tests, data management, regulatory records, and good clinical practice. Because of limited auditing visits, participating sites will be required to submit (either electronically or via paper) requested source documents to the Coordinator Center for source verification, at the Coordinator Center's request. In addition, appropriate regulatory documents should be sent electronically to the Coordinating Center in lieu of being collected at the time of the auditing visit.

9.3.2 Participating Institution

It is the participating institution's responsibility to notify the DF/HCC Lead Institution or designee of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve the DF/HCC Multi-Center Protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the DF/HCC Lead Institution or designee within 12 weeks after the audit date.

9.3.3 Coordinating Center (Lead Institution or Designee)

The Protocol Chair will review all DF/HCC Multi-Center Protocol Final Audit reports and corrective action plans if applicable. The Lead Institution or designee must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the Protocol Chair to implement recommendations or require further follow-up. For unacceptable audits, the Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

9.4 Sub-Standard Performance

The Protocol Chair, DFCI IRB and the NCI for CTEP trials, is charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center Protocol.

9.4.1 Corrective Actions: Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, and adherence to protocol requirements will be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Institutions that fail to demonstrate significant improvement will be considered by the Protocol Chair for revocation of participation.

APPENDIX H: DF/HCC Tumor Metrics Submission Procedures for non-DF/HCC Sites

All participants with measurable disease with partial or complete responses on trial should have their responses confirmed by the DF/HCC Tumor Imaging Metrics Core (TIMC). For patients with responses, the following materials should be submitted to the Dana-Farber Cancer Institute:

- Baseline CT/MRI study on CD
- CT/MRI documenting response on CD
- CT/MRI confirming response on CD
- Radiology reports from baseline CT/MRI and CT/MRIs in which response was documented and confirmed.

All materials should be sent to the Study Coordinator at the following address:

450 Brookline Ave, DA129
Dana-Farber Cancer Institute
Boston, MA 02215

APPENDIX I:

Family History Questionnaire

Instructions:

1. When completing this questionnaire, please be sure to complete all sections.
2. If there is not enough space to list all relatives, please include that information on a separate sheet of paper

Name: _____ (Last) (First) (Maiden) **Date of Birth:** _____ (MM/DD/YYYY) **Phone No: Home**: _____ **Work:** _____ **When is the best time to contact you?** ❑ Morning (❑Home ❑ Work) ❑ Afternoon (❑Home ❑ Work) ❑ Evening (❑Home ❑ Work)	**What best describes your family's ethnic heritage?** (ex. Irish, Jewish) **Mother's Family**_____ **Father's Family**_____ **Are you adopted?** ❑ Y ❑ N ❑ Unknown **Are you a twin?** ❑ Y ❑ N If Yes: ❑ Identical ❑ Same sex, unknown if identical ❑ Unknown

Please complete the following table for your parents and children even if they have not had cancer. If they have not had cancer, please write in "NONE" in the Cancer Type column. If they have had more than one type of cancer, please list all types and age at diagnosis of each cancer.

YOUR PARENTS AND CHILDREN

Relative and Name	Date of Birth	Cancer Type(s)	Age(s) @ Diagnosis	Date of Death
Father				
Mother				
Child #1 Sex M F				
Child #2 Sex M F				
Child #3 Sex M F				
Child #4 Sex M F				
Child #5 Sex M F				

Please complete the following table for your brothers and sisters even if they have not had cancer. If they have not had cancer, please write in "NONE" in the Cancer Type column. If they have had more than one type of cancer, please list all types and age at diagnosis of each cancer.

YOUR BROTHERS AND SISTERS

Relative and Name	Date of Birth	Cancer Type(s)	Age(s) @ Diagnosis	Date of Death
Brother #1 __Full __Half (same mother) __Half (same father)				
Brother #2 __Full __Half (same mother) __Half (same father)				
Brother #3 __Full __Half (same mother) __Half (same father)				
Brother #4 __Full __Half (same mother) __Half (same father)				
Sister #1 __Full __Half (same mother) __Half (same father)				
Sister #2 __Full __Half (same mother) __Half (same father)				
Sister #3 __Full __Half (same mother) __Half (same father)				
Sister #4 __Full __Half (same mother) __Half (same father)				

Please complete the following table for your nieces and nephews (children of your brothers and sisters) even if they have not had cancer. If they have not had cancer, please write in "NONE" in the Cancer Type column. If they have had more than one type of cancer, please list all types and age at diagnosis of each cancer.

NIECES AND NEPHEWS

Relative and Name of Parent	Date of Birth	Cancer Type(s)	Age(s) @ Diagnosis	Date of Death
Niece/Nephew #1 Name of Parent				
Niece/Nephew #2 Name of Parent				
Niece/Nephew #3 Name of Parent				
Niece/Nephew #4 Name of Parent				
Niece/Nephew #5 Name of Parent				
Niece/Nephew #6 Name of Parent				
Niece/Nephew #7 Name of Parent				
Niece/Nephew #8 Name of Parent				
Niece/Nephew #9 Name of Parent				
Niece/Nephew #10 Name of Parent				
Niece/Nephew #11 Name of Parent				
Niece/Nephew #12 Name of Parent				

Please complete the following table for your grandparents, aunts, and uncles on your **FATHER's** side even if they have not had cancer. If they have not had cancer, please write in "NONE" in the Cancer Type column. If they have had more than one type of cancer, please list all types and age at diagnosis of each cancer.

GRANDPARENTS, AUNTS, and UNCLES ON YOUR FATHER'S SIDE

Your Father's Side				
Relative	**Date of Birth**	**Cancer Type(s)**	**Age(s) @ Diagnosis**	**Date of Death**
Grandfather				
Grandmother				
Uncle #1				
Uncle #2				
Uncle #3				
Uncle #4				
Uncle #5				
Aunt #1				
Aunt #2				
Aunt #3				
Aunt #4				
Aunt #5				

Please complete the following table for your grandparents, aunts, and uncles on your **MOTHER's** side even if they have not had cancer. If they have not had cancer, please write in "NONE" in the Cancer Type column. If they have had more than one type of cancer, please list all types and age at diagnosis of each cancer.

GRANDPARENTS, AUNTS, and UNCLES ON YOUR MOTHER'S SIDE

Your Mother's Side				
Relative	**Date of Birth**	**Cancer Type(s)**	**Age(s) @ Diagnosis**	**Age @ Death**
Grandfather				
Grandmother				
Uncle #1				
Uncle #2				
Uncle #3				
Uncle #4				
Uncle #5				
Aunt #1				
Aunt #2				
Aunt #3				
Aunt #4				
Aunt #5				

Please complete the following table for your cousins (children of your aunts and uncles) on your **FATHER'S** side even if they have not had cancer. If they have not had cancer, please write in "NONE" in the Cancer Type column. If they have had more than one type of cancer, please list all types and age at diagnosis of each cancer.

COUSINS ON YOUR FATHER'S SIDE

Relative and Name of Parent	Date of Birth	Cancer Type (s)	Age(s) @ Diagnosis	Date of Death
Cousin #1 Sex M F Name of Parent				
Cousin #2 Sex M F Name of Parent				
Cousin #3 Sex M F Name of Parent				
Cousin #4 Sex M F Name of Parent				
Cousin #5 Sex M F Name of Parent				
Cousin #6 Sex M F Name of Parent				
Cousin #7 Sex M F Name of Parent				
Cousin #8 Sex M F Name of Parent				

Please complete the following table for your cousins (children of your aunts and uncles) on your **MOTHER'S** side even if they have not had cancer. If they have not had cancer, please write in "NONE" in the Cancer Type column. If they have had more than one type of cancer, please list all types and age at diagnosis of each cancer.

COUSINS ON YOUR MOTHER'S SIDE

Relative and Name of Parent	Date of Birth	Cancer Type(s)	Age(s) @ Diagnosis	Date of Death
Cousin #1 Sex M F Name of Parent				
Cousin #2 Sex M F Name of Parent				
Cousin #3 Sex M F Name of Parent				
Cousin #4 Sex M F Name of Parent				
Cousin #5 Sex M F Name of Parent				
Cousin #6 Sex M F Name of Parent				
Cousin #7 Sex M F Name of Parent				
Cousin #8 Sex M F Name of Parent				

Please complete the following table for other relatives we have not asked about on your **FATHER's** side even if they have not had cancer. If they have not had cancer, please write in "NONE" in the Cancer Type column. If they have had more than one type of cancer, please list all types and age at diagnosis of each cancer.

OTHER RELATIVES ON YOUR FATHER'S SIDE

Your Father's Side				
Relative	**Date of Birth**	**Cancer Type(s)**	**Age(s) @ Diagnosis**	**Date of Death**
Other Relative #1 Sex M F				
Other Relative #2 Sex M F				
Other Relative #3 Sex M F				
Other Relative #4 Sex M F				

Please complete the following table for other relatives we have not asked about on your **MOTHER's** side even if they have not had cancer. If they have not had cancer, please write in "NONE" in the Cancer Type column. If they have had more than one type of cancer, please list all types and age at diagnosis of each cancer.

OTHER RELATIVES ON YOUR MOTHER'S SIDE

Your Mother's Side				
Relative	**Date of Birth**	**Cancer Type(s)**	**Age(s) @ Diagnosis**	**Date of Death**
Other Relative #1 Sex M F				
Other Relative #2 Sex M F				
Other Relative #3 Sex M F				
Other Relative #4 Sex M F				