SUMMARY OF CHANGES

For Protocol Amendment #11 to: 9974

NCI Protocol #: 9974
Local Protocol #: 17-732

NCI Version Date: 13 May 2019
Protocol Date: 13 May 2019

I. Protocol Changes following Request for Rapid Amendment

#	*Section*	*Page(s)*	*Change*
1	ICD	-	The informed consent document was modified as a result of the CTEP RRA for Olaparib and latest version of the CAEPR. The protocol version date was also updated in the consent document.
2	Protocol document	-	The protocol version date was updated on the cover page and throughout the protocol document. Minor typographical revisions were made throughout the protocol document. These changes are tracked.

3	7.1	69	The Comprehensive Adverse Events and Potential Risks Lists (CAEPRs) were updated to reflect the latest CAEPR for Olaparib (Version 2.4, April 24, 2019). These changes are a result of the CTEP RRA for Olaparib.
			
			The following changes were made to the CAEPR:
			• Increase in Risk Attribution:
			  • Changed to Rare but Serious from Also Reported on Cediranib Trials But With Insufficient Evidence for Attribution: Platelet count decreased; White blood cell decreased
			• Provided Further Clarification:
			  • A new note has been added to the CAEPR; "NOTE: New Primary Malignancies other than MDS/AML New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented BRCA mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib."

NCI Protocol #: *9974*

Local Protocol #: 17-732

ClinicalTrials.gov Identifier: NCT02899728

TITLE: A phase II study of olaparib plus cediranib in combination with standard therapy for small cell lung cancer

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

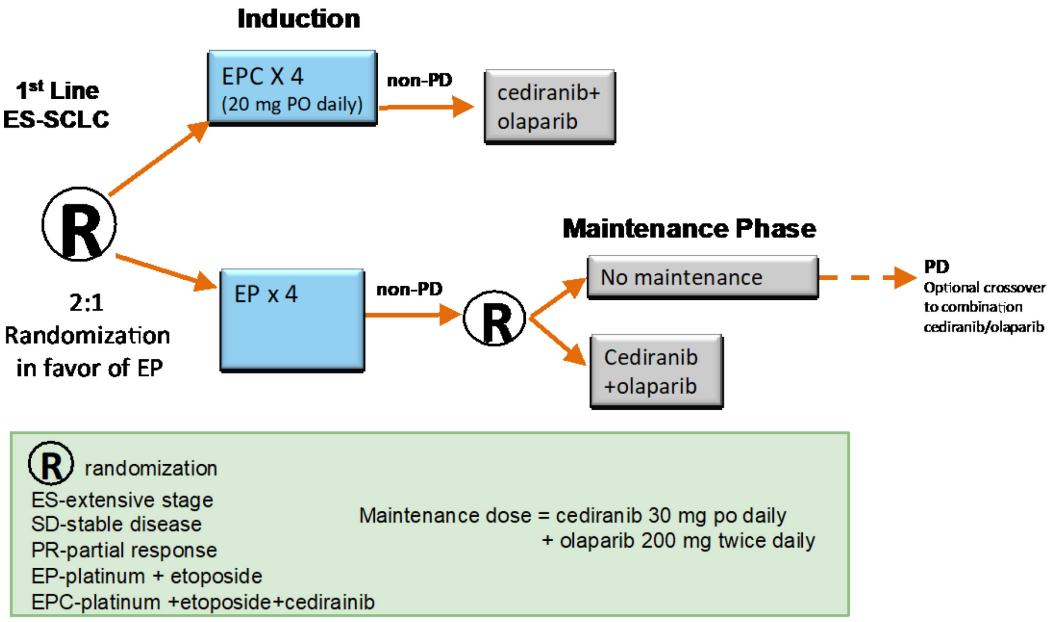
Other Agent(s): Cisplatin (Commercial), Carboplatin (Commercial), Etoposide (Commercial)

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Original / Version 5 / 04 April 2017
Amendment 3 / Version 6 / 03 October 2017
Amendment 4 / Version 7 / 18 October 2017
Amendment 6 / Version 8 / 21 May 2018
Amendment 7 / Version 9 / 31 Jul 2018
Amendment 8 / Version 10 / 12 Oct 2018
Amendment 9 / Version 11 / 11 Jan 2019
Amendment 10 / Version 12 / 17 Jan 2019
Amendment 11 / Version 13 / 13 May 2019

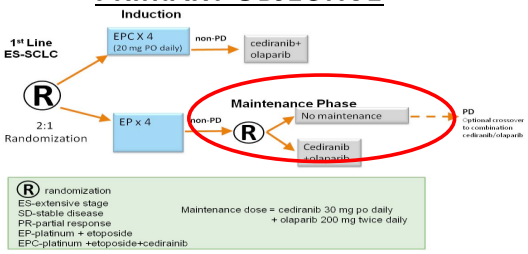
SCHEMA

OVERALL SCHEMA



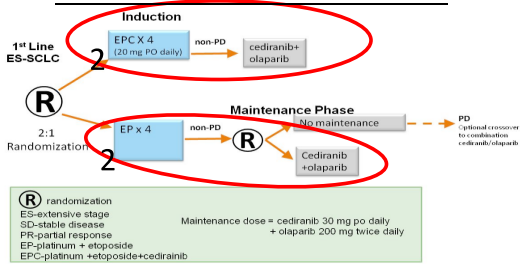
PLANNED OBJECTIVES

PRIMARY OBJECTIVE

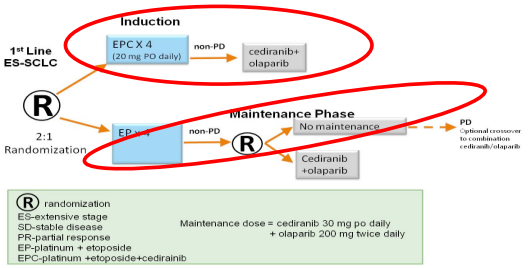


Maintenance vs. no maintenance

SECONDARY COMPARISONS



Cediranib in initial therapy vs. standard



Full standard of care regimen vs. new initial therapy/maintenance

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1. OBJECTIVES

1.1 Primary Objectives

To determine whether the addition of cediranib plus olaparib as maintenance therapy, in patients with small cell lung cancer (SCLC) who have stable disease or better (non-progressive disease or non-PD) after initial therapy, leads to improved median progression-free survival (PFS). PFS is measured in months from the time of randomization to maintenance therapy (after completion of initial therapy), compared to standard therapy (no maintenance treatment).

1.2 Secondary Objectives

To evaluate the impact of cediranib plus olaparib maintenance therapy on median overall survival (OS) in patients with SCLC who have non-PD after initial therapy. The groups compared are 1) those randomized to EP and subsequently randomized to OC maintenance and 2) those randomized to EP and subsequently randomized to no maintenance.

To determine whether the addition of cediranib to cisplatin/carboplatin plus etoposide during initial therapy adds benefit to response rate, median PFS and median OS. PFS and OS are measured in months from the time of randomization to initial therapy. The groups compared are 1) those randomized to EPC followed by maintenance and 2) those randomized to EP initial therapy AND subsequently randomized to OC maintenance therapy.

To assess safety and tolerability of the combination of cediranib plus olaparib during maintenance therapy.

To evaluate potential biomarkers of clinical benefit to olaparib/cediranib combination, including tumor proteomic and genomic markers, and circulating levels of cytokines and angiogenic factors, that that may be associated with clinical benefit.

2. BACKGROUND

2.1 Small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related death in the United States and more people die of lung cancer than from breast, colon, and prostate cancer combined(1). SCLC is an aggressive tumor that represents approximately 13 percent of all lung cancer in the US(2). This disease has a dismal outcome that has improved only marginally in the last 30 years(3). Although it is a chemotherapy- and radiotherapy-sensitive tumor, SCLC continues to show very high rates of relapse and metastasis, resulting in a very poor prognosis. The high propensity for metastases and poor outcomes in this tumor type underscore the need to develop therapies with more durable benefit and that may block not only tumor growth, but also invasion and the development of distant metastases.

Angiogenesis inhibitors have been studied in SCLC with this goal in mind and have had encouraging hints of activity. Several angiogenesis inhibitors have shown a significant stable disease rate as later line therapy, including pazopanib (52% stable disease [SD] rate)(4), sunitinib (30% SD rate)(5), and cediranib (36% SD rate)(6). Tyrosine kinase inhibitors (TKIs) have also demonstrated promising activity in SCLC when given in combination with chemotherapy or in the maintenance setting. In a phase I study, we found that cediranib, a TKI targeting VEGFR, PDGFR, and c-KIT, was tolerable when given at a dose of 20 mg or 30 mg daily in combination with etoposide and cisplatin (EP). The combination was found to have an objective response rate (ORR) in excess of 70 percent and a PFS rate of 8.9 months in SCLC patients receiving 20 mg daily(7) (Heymach et al, in preparation). A similar TKI, sunitinib, was found to be safe and to significantly prolong PFS when used as maintenance therapy after EP chemotherapy with a median PFS of 3.7 months for sunitinib vs. 2.1 months for placebo (PFS HR 1.62, P=0.02)(8). A trend toward longer overall survival was also demonstrated in limited-stage SCLC patients in a trial of vandetanib maintenance after chemotherapy (HR 0.45, one sided P=0.07)(9).

There are currently no validated biomarkers for VEGFR TKIs in routine clinical use, although several promising candidates have been identified. We and others have shown that circulating levels of plasma cytokines and angiogenic factors (CAFs) as well as germline genetic variations in angiogenic and inflammatory genes may be predictive markers for benefit or the emergence of therapeutic resistance(10-14). Notably, through the testing and validation using samples from two randomized placebo controlled studies of the VEGFR TKI pazopanib, an agent with a similar spectrum as cediranib, we identified IL-6 as a predictive marker of benefit for pazopanib(10). This included validation studied using CLIA-certified assays. We have also identified plasma HGF and bFGF as markers associated with the emergence of therapeutic resistance from patients treated with chemotherapy plus bevacizumab(11) and circulating VEGF as predictive marker of PFS benefit for the VEGFR TKI vandetanib(12). Germline genetic variations have also been associated with response and toxicities after treatment with bevacizumab(13).

Proteomic profiling was performed on a large panel of SCLC cell lines which led to the observation that PARP1 and several other DNA repair proteins are expressed at high levels in SCLC(15). PARP1 over-expression was confirmed in patient tumors at the protein level by immunohistochemistry (IHC) and at the mRNA level. Based on this finding, several PARP inhibitors were tested in pre-clinical models of SCLC. Olaparib, rucaparib, and talazoparib (previously BMN-673) all demonstrated striking single agent activity in a majority of SCLC cell lines tested. Furthermore, the addition of a PARP inhibitor to standard chemotherapies (e.g., cisplatin, etoposide and/or topotecan) and radiation further potentiated their effect(15, 16). In animal models including xenografts and patient-derived xenografts (PDXs), talazoparib has demonstrated significant anti-tumor activity as a single agent, comparable or superior to cisplatin(17),(18). Based on these observations, several clinical trials were initiated to investigate the effects of PARP inhibition in SCLC patients. In the first study to complete enrollment, single-agent talazoparib (BMN-673) was tested in patients with platinum-sensitive SCLC relapse (NCT01286987). Preliminary data demonstrated 2 out of 23 patients with RECIST confirmed partial responses (PRs) and 3 out of 23 with SD > 24 weeks (clinical benefit rate of 25%). More than half of patients treated had some tumor volume reduction as their best response(19). Currently, there are two studies investigating the use of veliparib (ABT-888) in

combination with standard frontline chemotherapy (NCT01642251 and NCT02289690). E2511 (NCT01642251) is a phase I/II trial of cisplatin, etoposide, and veliparib in treatment naïve SCLC patients. Phase I data from this study support the safety and tolerability of the combination, with partial or complete responses observed in 5 out of 7 evaluable patients(20).

To date, the activity of PARP inhibitors is best established in cancers with mutations in BRCA1/2 and other DNA repair genes that result in synthetic lethality in the setting of PARP inhibition. In fact, olaparib monotherapy was FDA approved last year for patients with advanced BRCA-mutated ovarian cancer. In SCLC, their mechanism of action and identification of potential PARP inhibitor biomarkers is an area of active investigation. Likely the universal loss of RB1, with resulting dependence on E2F1, plays a role. It has been demonstrated that expression levels of several DNA repair proteins – both individually and as a "DNA repair signature" – are associated with response in pre-clinical models of lung cancer(21).

Rationale for combination of angiogenesis inhibition with PARP inhibition in SCLC

Several lines of preclinical evidence support the combination of a PARP inhibitor and anti-angiogenic therapy. While the role of DNA damage repair pathways in tumors treated with anti-angiogenic therapies is not well understood, the hypoxic state is known to result in genetic instability and mutagenesis. It is known that hypoxia triggers a DNA damage response(22), resulting in p53 accumulation and eventual apoptosis; p53-deficient tumors suppressed the apoptotic effect, promoting tumor survival in spite of the hypoxic state(23). However, despite the presence of DSB markers such as histone gH2AX, there is little evidence of DNA damage during the hypoxic state, and gH2AX staining is atypical (diffuse rather than punctate), though severe hypoxia may result in aberrant replication complexes, single-strand breaks, and regions of single-stranded DNA(24). After re-oxygenation, double-strand breaks are noted to accumulate, and tumor survival is dependent upon intact DNA repair complexes(25). Thus, post-hypoxic tumor cells which rely upon angiogenic signaling may also be vulnerable to PARP inhibition.

Human breast (MCF-7) and lung adenocarcinoma (A549) cell lines grown under hypoxic conditions exhibit severely reduced levels of BRCA1 and RAD51 due to transcriptional downregulation(26, 27). Subsequent work determined that chemical PARP inhibitors displayed increased cytotoxicity against A549, RKO (colon), and H460 (lung) cell lines under hypoxic conditions, compared to normoxic conditions(28). Exposure to PARP inhibitors or PARP-1 RNAi downregulated BRCA1 and RAD51 expression in a dose-dependent manner, regardless of oxygenation, and the addition of hypoxic conditions to PARP inhibition enhanced the downregulatory effect.

In addition, studies in primary human umbilical vein endothelial cells (HUVECs) and immortalized human endothelial cell lines demonstrate a connection between hypoxia-driven angiogenesis and DNA repair, and show that inhibition of DNA repair pathways can inhibit endothelial cell proliferation. In HUVECs treated under a hypoxic state, gH2AX foci are found primarily in proliferating endothelial cell populations (positive staining for proliferative cell nuclear antigen) where they co-localize with replication protein A, suggesting a replication stress-related origin of hypoxia-induced gH2AX foci(29). Small interfering RNA (siRNA) knockdown of the replication stress-induced ataxia teleangiectasia mutated kinase (ATM)- and

Rad3-related kinase (ATR) pathway, but not the ATM pathway, inhibited gH2AX formation, and siRNA knockdown of gH2AX significantly decreased growth factor-induced proliferation and fetal calf serum-induced HUVEC proliferation under hypoxic conditions. PARP inhibition (via the specific small-molecule inhibitor GPI 15427) inhibited angiogenesis in matrigel *in vitro (30)*. At drug levels that did not affect endothelial cell proliferation (0.1-1 mcM), PARP inhibition reduced the formation of tube-like structures and inhibited platelet-derived growth factor (PlGF)- and VEGF-induced endothelial cell migration. At 1 mcM, GPI 15427 did not inhibit hypoxia-inducible factor 1a (HIF-1α) induction by the hypoxia mimetic agent $CoCl_2$, indicating that PARP inhibition's effects on migration were not exerted through influencing HIF-1a function.

Collectively, the evidence indicates that anti-angiogenic therapy may complement PARP inhibition, and also suggest that the combination of cediranib and olaparib may synergize not only with regard to direct antitumor activity but also with regard to their anti-angiogenic effect on tumor vasculature.

Given the striking clinical benefit of this combination seen in ovarian cancer, the known clinical activity of anti-angiogenic agents in SCLC as well as the potential activity of PARP inhibition in SCLC based on pre-clinical data and emerging clinical data, there is potential for improved efficacy with the combination of these two classes of drugs in SCLC as well. The effect of combination olaparib plus cediranib as maintenance therapy following first-line chemotherapy (± cediranib) for extensive-stage SCLC will be evaluated to determine whether synergistic prolongation of PFS is possible in SCLC, a tumor type with 60-80 percent responses to first-line chemotherapy but PFS of only 3 months post-first line treatment.

2.2 CTEP IND Agents

2.2.1 Cediranib (AZD2171)

Cediranib (AZD2171, Recentin™; 4-[(4-fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy) quinazoline maleate; AZD2171 maleate) is a member of an emerging class of novel orally administered small molecule vascular endothelial growth factor (VEGF) receptor TKI with anti-angiogenic properties (31, 32).

Investigators should be familiar with the current cediranib IB.

2.2.1.1 Mechanism of Action

VEGF is a key angiogenic factor, and has been implicated in tumor blood vessel formation and in disease progression in a range of solid tumor malignancies (33). Two high-affinity VEGF transmembrane receptors (VEGFRs) with associated TK activity have been identified on human vascular endothelium, VEGFR-1 (also known as fms-like tyrosine kinase 1 or Flt-1) and VEGFR-2 (also known as kinase insert domain-containing receptor or KDR) (34). VEGFR-1 and VEGFR-2 signaling help mediate tumor progression. Cediranib has been developed as a potent inhibitor of VEGFR-1 and VEGFR-232. Cediranib also has activity against VEGFR-3 and c-Kit.

Cediranib is expected, with chronic oral dosing, to inhibit VEGF-driven angiogenesis and as a result prevent the progression and metastasis of solid tumors, and may have broad-spectrum clinical utility.

2.2.1.2 Summary of Non-Clinical Efficacy Studies

The effect of cediranib was studied in athymic nu/nu mice bearing established subcutaneous human tumor xenografts of diverse histologies [SW620 (colon), PC-3 (prostate), Calu-6 (lung), SKOV-3 (ovarian), and MDA-MB-231 (breast)]. Animals were administered cediranib orally at doses from 0.75-6 mg/kg/day (2.25-18 mg/m2/day) in a constant volume of 0.1 mL/10 g body weight for 24-28 days. Cediranib produced a statistically significant inhibition of tumor growth in all human tumor types examined when dosed at 1.5 mg/kg/day (4.5 mg/m2/day) or higher.

The murine renal cell carcinoma (RENCA) model, which rapidly (generally within 10 days) metastasizes to the lung and abdominal lymph nodes, has also been used for cediranib efficacy studies. In experiments incorporating a vehicle control, 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 receptor TKI reported in the literature.

Using a transgenic mouse model in which multiple mammary tumors spontaneously develop after two pregnancies, investigators studied the temporal effects of cediranib administration. When dosed with cediranib (0.75- 6 mg/kg/day PO) at the time early lesions start to develop, the number of tumor foci was not affected, but their growth was inhibited. When tumors were well-established before cediranib was given (at doses of 3 and 6 mg/kg/day), dose-dependent growth inhibition occurred as well as tumor regression.

A full description of non-clinical efficacy studies can be found in the current version of the cediranib IB.

2.2.1.3 Summary of Non-Clinical Pharmacology and Toxicology

Nonclinical pharmacology and toxicology company-sponsored studies have been conducted in rats, dogs, and cynomolgus monkeys. In rats and dogs, oral bioavailability is high, but absorption is relatively slow, with Cmax of the agent seen 4-6 hours after PO dosing. Plasma concentrations and exposure are generally linear over the dose ranges studied in rats. Cediranib is excreted in the feces (>70% of the dose) of rats, dogs, and cynomolgus monkey after both PO and intravenous (IV) administration. Fecal excretion was the predominant route of elimination (>70% of the dose) in both rat, dog and cynomolgus monkey after both PO and IV administration. Elimination was rapid in rats and monkeys with over 75% of the dose being recovered in the first 48 hours; in dogs, excretion was slightly slower but again substantially complete by 7 days. Over the dose ranges examined in the rat, plasma concentrations and exposure generally increased in proportion to dose; however, in

monkeys, plasma cediranib concentration-time profiles obtained following a single PO dose indicated that systemic exposure increased in a greater than dose-proportional manner over the dose range 0.05-2.5 mg/kg.

Protein binding of cediranib (90-95%) was relatively high across all species examined and was independent of concentration (range: 0.03-10 mcg/mL) and gender. Cediranib was approximately 95% bound to human plasma proteins, with human serum albumin and α1-acid glycoprotein accounting for most of this binding.

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

Cediranib did not induce rat hepatic microsomal P450 activity but caused a 40-60% reduction in CYP1A activity at the 2.5 mg/kg dose level. Inhibition studies in vitro using human hepatic microsomal protein gave IC50 values for cediranib against CYP2D6, CYP3A4 testosterone, and CYP3A4 midazolam of 32.9, 16.2, and 21.4 mcg/mL, respectively. For CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1, the IC50 values were outside the concentration range of cediranib examined. As the clinically relevant plasma concentration of cediranib has not yet been determined, any possible effect on compound clearance and drug interaction is currently unknown.

A full description of non-clinical pharmacology and toxicology can be found in the current version of the cediranib IB.

2.2.1.4 Summary of Clinical Pharmacokinetics and Pharmacodynamics

Preliminary pharmacokinetics (PK) information indicates a time to maximum serum concentration (Tmax) of 2 hours (range, 2-6 hours), a Cmax of 107.8 ± 29.8 ng/mL, and a half-life (t1/2) of 12.1 ± 2.2 hours.

Preliminary information on blood biomarkers in glioblastoma patients indicates that plasma VEGF, placental growth factor (PLGF), and stromal cell-derived factor 1α

(SDF1α) were increased after treatment, and plasma PIGF and VEGF decreased upon cediranib discontinuation. Plasma basic fibroblast growth factor (bFGF) and SDF1α and viable circulating endothelial cells (CECs) increased when tumors escaped treatment with cediranib(35).

Additional information on the relationship between clinical outcome and biomarkers has been reported for a DCTD-sponsored trial(36). Changes in vascular permeability/flow as measured by magnetic resonance imaging (MRI) methods (Ktrans), microvessel volume, and circulating collagen IV levels were determined. Of the 30 patients in the trial, all three parameters were reliably measured in 28. A greater eduction in Ktrans after one dose of cediranib was seen in patients with increased PFS (P=0.0015) and OS (P=0.0039). A greater increase in the calculated blood volume (CBV) of tumor microvessels after one dose of cediranib was seen in glioblastoma patients with extended OS (P=0.0056). A greater increase in collagen IV levels in plasma was detected in patients with extended PFS (P=0.0010). Peripheral blood was evaluated serially for VEGF concentration and CECs in another trial(6). A stark increase in CECs was noted at progression in several patients.

A full description of clinical pharmacokinetics and pharmacodynamics can be found in the current version of the cediranib IB.

2.2.1.5 Clinical Experience

AstraZeneca has sponsored 15 phase I studies of cediranib (single-agent or in combination with gefitinib, either FOLFOX, irinotecan [±cetuximab], pemetrexed or docetaxel, etoposide/cisplatin, or lomustine), 8 phase 2 studies (single-agent, or in combination with fulvestran, FOLFOX, or paclitaxel/carboplatin), one phase 2/3 study (cediranib plus bevacizumab), and two phase 3 studies (cediranib plus FOLFOX or XELOX and cediranib plus lomustine). Details of the studies, responses, and safety assessments are summarized in the Cediranib Investigator's Brochure.

Cediranib has been administered to patients in 38 DCTD, NCI-sponsored clinical trials. Complete responses (CRs) and partial responses (PRs) have been reported in clinical trials of cediranib in solid tumors such as NSCLC(37), renal cell carcinoma (RCC)(38), prostate(39), mesothelioma(40), and gynecologic tumors (41, 42).

The maximum tolerated dose (MTD) for cediranib in combination with 75 mg/m2 temozolomide and radiation was established at 30 mg/day in patients with newly-diagnosed glioblastoma, with no dose limiting toxicities (DLTs) observed. Cediranib was then administered at 45 mg/day in a post-radiation setting, and in addition to the expected AEs of hypertension, fatigue and palmar/plantar erythema, one patient discontinued due to grade 3 transaminase elevation and one patient required dose reduction to 15 mg/day due to proteinuria. Median PFS was 288 days (95% CI 240–∞) and median OS was 786 days (95% CI 411–∞); these values were improvements over historical controls. Best radiographic response in patients who completed

chemoradiotherapy was CR in two patients, PR in 20 patients, and stable disease (SD) in 15 patients. Patients with increased tumor perfusion during chemoradiotherapy survived nearly 1 year longer (mean OS 611 days) than patients with decreased perfusion (mean OS 269 days).

Among 31 patients in a phase 2 trial of cediranib in recurrent glioblastoma, radiographic PRs (>50% volume reduction) were reported in 17 patients, and minor responses (25-50% volume reduction) in an additional 6 patients(35). Median PFS was 117 days, and median OS was 227 days. Additionally, cediranib alleviated brain edema, a major cause of morbidity in glioblastoma patients(35). DLTs were observed in 9 of the 16 patients with hypertension; fatigue and diarrhea were seen most often.

Two phase II trials of cediranib at two different dose levels (30 mg/day and 45 mg/day) in patients with unresectable locally advanced or metastatic hepatocellular carcinoma (HCC) yielded no objective responses(43, 44). Grade 3 AEs were observed in 93% of patients receiving 45 mg/day. Fatigue, hypertension, and anorexia accounted for the majority of the AEs.

Response information for 45 of 46 patients on a trial of cediranib in malignant pleural mesothelioma reported PR by RECIST in 4/47 patients (9%), including 2 patients with bulky disease who had 56% and 91% tumor shrinkage; and 16/47 (34%) had SD44. Median PFS was estimated at 2.56 months, median OS at 9.5 months. The most common non-hematologic AEs were hypertension (70%), fatigue (64%), and diarrhea (64%).

Among 47 evaluable patients receiving cediranib in a trial in ovarian, primary peritoneal serous, or fallopian tube cancer, the clinical benefit rate was 30%; eight patients had a PR and six had SD; there were no CRs (41). Median PFS was 5.2 months, and median OS had not been reached after a median follow-up time of 10.7 months. Grade 4 AEs included CNS hemorrhage, lipase, and hypertriglyceridemia/hypercholesterolemia/elevated lipase, and dehydration/elevated creatinine. Grade 3 AEs include hypertension, fatigue, and diarrhea. Hypertension occurred in 87% of the patients by the end of the study; in 43%, it was grade ≥351. Grade 2 hypothyroidism occurred in 43% of patients.

Preliminary information from 60 patients in a phase II trial of cediranib in persistent ovarian, peritoneal, or fallopian tube cancer has been reported(42). Patients were divided into those whose disease was found to be platinum-resistant and those whose disease was platinum-sensitive in a prior therapy regimen. Response and prolonged SD rate was 41% for platinum-sensitive and 29% for platinum-resistant patients, respectively. In the platinum-sensitive group, there were two confirmed PRs and one unconfirmed PR, while one unconfirmed PR was observed in the platinum resistant arm. Median time to progression (TTP) and median survival for all patients was 4.1 months and 11.9 months, respectively, with no significant differences between the platinum-sensitive and -resistant groups. The most frequent AEs were fatigue, diarrhea, hypertension, and anorexia, while hypertension and fatigue were the most

frequent grade 3 or higher AEs. Sixteen patients required dose reduction to 30 mg and 20 mg.

Information on 59 patients in a trial of cediranib in metastatic androgen-independent prostate cancer has been reported(39). A total of 59 patients were enrolled, of whom 67% had received two or more previous chemotherapy regimens. Six of 39 patients with measurable disease had confirmed PRs and one had an unconfirmed PR. At 6 months, 43.9% of patients were progression-free; the median PFS and OS periods for all patients were 3.7 months and 10.1 months, respectively. Decreases in lymph node metastases as well as in lung, liver, and bone lesions were observed. Grade 3 AEs included vomiting, prolonged QTc interval, muscle weakness, weight loss, dehydration, fatigue, hypoxia, renal failure, transaminitis, and anorexia.

Thirty-two of 43 patients enrolled in a trial of cediranib in renal cell carcinoma (RCC) are evaluable for response(38). PRs were observed in 12 patients, SD in 15, and PD in 5. Median PFS was 8.7 months and the 6-month progression-free proportion was 63%. Treatment-related grade 3 or higher AEs included hypertension, fatigue, joint pain, abdominal pain, and dyspnea.

Cediranib was administered in a phase II trial in small cell lung cancer (SCLC), in which one unconfirmed PR and eight SD were noted(6). Salient AEs were fatigue (four grade 3, two grade 4), and grade 3 diarrhea, skin rash, proteinuria, transaminitis, muscle weakness, and hypertension. However, the original 45 mg/day dose was not tolerable in the patient population, and the modest activity seen at 30 mg/day did not support the use of cediranib as monotherapy for SCLC.

A combination trial of cediranib plus docetaxel, doxorubicin, and cyclophosphamide in advanced breast cancer accrued only two patients, and was closed due to systolic dysfunction that occurred with concurrent cediranib and doxorubicin.

Another combination trial of cediranib plus pemetrexed in NSCLC divided patients into two arms—those who had not received bevacizumab in prior chemotherapy regimens (Cohort A), and those who had (Cohort B)(37). The confirmed response rate was 16% (10% Cohort A, 25% Cohort B), and the disease control rate (CR/PR/SD) was 71% (74% Cohort A, 67% Cohort B). Grade 3/4 AEs included neutropenia, febrile neutropenia, fatigue, diarrhea, hypertension, anorexia, cardiac ischemia, bronchopleural fistula, and esophagitis. Of the 17 patients who received cediranib for 4 cycles, 71% required dose reduction from 30 mg/day, and of the 18 patients who received pemetrexed for 4 cycles, 22% required dose reduction.

2.2.1.6 Adverse Events and Recommended Dosing

The most frequently reported AEs for cediranib on company-sponsored trials were fatigue, diarrhea, nausea, vomiting, hoarseness, hand-foot syndrome, and hypertension. Hypertension is an expected pharmacologic effect of agents that inhibit VEGF, and is one of the most common adverse events (AEs) reported in trials of

cediranib. Dose-related increases in thyroid stimulating hormone (TSH) and decreases in total thyroxine have been observed at doses of 30 mg and above, and are most marked at 60 mg.

The recommended dose for cediranib monotherapy is 30 mg/day; the recommended dose in combination with chemotherapy agents is 20 mg/day, although exceptions to these doses may be appropriate in other studies, depending on age, patient population, tumor type, or agent(s) given in combination with cediranib (82).

2.2.2 Olaparib (AZD2281)

Olaparib is an inhibitor of the polyadenosine 5' diphosphoribose [poly(ADP-ribose)] polymerase enzymes, PARP-1 (IC50 = 5nM), PARP-2 (IC50 = 1nM), and PARP-3 (IC50 = 4nM), which is being developed as an oral monotherapy (including maintenance) as well as for combination therapy with chemotherapy, ionizing radiation and other anti-cancer agents including novel agents and immunotherapy.

Investigators should be familiar with the current olaparib IB.

2.2.2.1 Mechanism of Action

PARP enzymes are involved in post-translational modification of histones and other nuclear proteins that contribute to the survival of cells following DNA damage and are essential for repairing DNA single strand breaks. PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms, as inhibition of PARPs leads to the persistence of single strand breaks, which can then be converted to the more serious DNA double strand breaks during the process of DNA replication. In normal cells, these double strand breaks can be efficiently repaired during cell division by homologous recombination repair (HR). HR is a process involving ATM (a major DNA double strand break signaling kinase, the 'MRN' nuclease protein complex; including Meiotic Recombination 11Homolog A [MRE11A], human RAD50 homolog [RAD50], and other homologous recombination DNA repair proteins such as RAD51, BRCA1 and BRCA2). Tumors exhibiting HR deficiencies (HRD), such as serous ovarian cancers and other tumor types with mutations in genes such as BRCA1/2, RAD51C, RAD51D, ATR, ATM, or Fanconi Anemia pathway members, cannot accurately repair the DNA damage, which may become lethal to cells as DNA damage accumulates. In these tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

2.2.2.2 Summary of Non-Clinical Efficacy Studies

Pre-clinical studies show cytotoxicity and anti-tumor activity following treatment with olaparib in cell lines and mouse tumor models with deficiencies in BRCA 53 as well as primary explant models and BRCA knock-out models, either as monotherapy

or in combination with established chemotherapies. Cytotoxicity of olaparib may involve inhibition of PARP enzymatic activity in addition to increased formation of PARP-DNA complexes, resulting in disruption of cellular homeostasis and cell death. PARP inhibitors such as olaparib may also enhance the DNA damaging effects of chemotherapy(45-47). Non-clinical studies looking at combinations of olaparib with chemotherapies such as alkylating agents, topoisomerase I inhibitors, platinum agents and taxanes, have additive to synergistic effects. For example, attenuation of PARP activity by PARP inhibitors leads to the chemopotentiation of topotecan, irinotecan and cisplatin cytotoxicity in both in vitro and in vivo models(45, 48-52). These studies highlight the importance of olaparib both as monotherapy and as part of combination therapy.

A full description of non-clinical efficacy studies can be found in the current version of the olaparib IB.

2.2.2.3 Summary of Non-Clinical Toxicology

In repeat dose oral toxicity studies of up to six months duration in rats and dogs, the principal target organ for toxicity was the bone marrow, with associated changes in peripheral hematology parameters. All changes showed full or partial recovery following withdrawal of olaparib. These effects of olaparib may be related to the pharmacology and mechanism of action of olaparib as an inhibitor of PARP-1 and PARP-2, as PARP-2 has been shown to play a role in hematopoietic stem/progenitor cell survival in both steady-state conditions and in response to stress(53).

In an Ames bacterial mutation test, olaparib was not mutagenic, but was clastogenic in an in vitro CHO chromosome aberration test. Oral dosing of olaparib also induced micronuclei in bone marrow of rats. These findings are consistent with genomic instability resulting from the primary pharmacology of olaparib.

In reproductive toxicology studies in rats, there were no adverse effects on male fertility following oral dosing of olaparib prior to mating. In female rats, conception rates were unaffected by pre- and peri-conception dosing. However, embryo-fetal survival was decreased and administration of olaparib during organogenesis had an adverse effect on embryo-fetal survival and increased major fetal malformations at dose levels that were not maternally toxic. These effects on embryo-fetal development are considered to be related to the pharmacology of olaparib. Exposures in the both the repeat dose and reproductive toxicology studies were generally below those achieved at the clinically therapeutic doses of 400 mg BID olaparib (capsule) and 300 mg BID (tablet).

Combination studies performed in rats suggest the potential for olaparib to exacerbate the effects of temozolomide and topotecan; however olaparib in combination with these anti-cancer agents did not induce any additional target organ toxicities compared to those seen with single agents.

A full description of non-clinical toxicology can be found in the current version of the olaparib IB.

2.2.2.4 Summary of Clinical Pharmacokinetics

Oral absorption of olaparib is rapid with peak plasma concentrations typically achieved between one and three hours after dosing. No marked accumulation was found with multiple dosing (accumulation ratio of 1.4-1.5 for twice daily dosing), with steady state exposures achieved within three to four days. Limited data suggests that systemic exposure (AUC) of olaparib increases less than proportionally with doses over a range of 100 to 400 mg, though PK data were variable across clinical trials. Co-administration with a high fat meal slowed the rate of absorption (Tmax delayed by 2 hours), but did not significantly alter the extent of olaparib absorption (mean AUC increased by approximately 20%).

Olaparib has a mean apparent volume of distribution at steady state of 167 ± 196 L after a single 400 mg dose. The in vitro protein binding at plasma concentrations achieved after 400 mg twice daily dosing is approximately 82%. Olaparib is metabolized primarily by CYP3A4. After a single 400 mg dose of olaparib, a mean terminal plasma t1/2 of 11.9 ± 4.8 hours and apparent plasma clearance of 8.6 ± 7.1 L/h were observed.

A full description of clinical pharmacokinetics can be found in the current version of the olaparib IB.

2.2.2.5 Summary of Clinical Experience

Olaparib has undergone a number of Phase I, II, and III clinical trials in a variety of tumor types enriched for those with HR deficiency, including BRCA- mutated cancers. Specifically, monotherapy studies have focused on BRCA1/2 associated ovarian cancer, BRCA1/2 associated breast cancer, a number of phase I studies in solid tumors, and phase II and III studies in BRCA mutated pancreatic cancer and MSI positive colorectal cancer. A number of Phase I and II clinical trials of olaparib in combination with chemotherapy and targeted agents including cisplatin, topotecan, gemcitabine, paclitaxel, and bevacizumab are currently ongoing or completed.

As of 15 December 2016, approximately 6558 patients are estimated to have received olaparib in the clinical programme including AstraZeneca-sponsored studies (3923 patients), a MAP (676 patients), ISSs and collaborative group studies (1959 patients). An estimated 4475 patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumours are estimated to have received treatment with olaparib in AstraZeneca-sponsored, interventional studies (3799 patients) and the MAP (676 patients). Since 2012/2013, most new clinical studies have utilized the tablet

formulation which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. Of the 4475 patients, 2109 received the capsule formulation, 2341 received the tablet formulation, and 25 received both capsule and tablet. In the AstraZeneca-sponsored, interventional studies, olaparib was given either as monotherapy (2618 patients) or in combination with chemotherapy or other anti-cancer agents, including studies where patients received monotherapy and combination therapy sequentially (n=1181).

Data from the available pre-clinical studies and subsequent clinical development programme demonstrate that olaparib appears to be active and generally well tolerated in patients with solid tumors including those with BRCA mutated cancers. In ovarian cancer, responses have been seen in all patient groups, including platinum resistant and refractory cancer.

From the available data to date in patients with advanced cancer, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure.

Adverse laboratory findings and/or clinical diagnoses considered to be associated with administration of olaparib monotherapy include haematological effects (anaemia, neutropenia, lymphopenia, thrombocytopenia, MCV elevation and increase in blood creatinine), nausea and vomiting, decreased appetite, diarrhoea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), headache and dizziness. Most of these events were generally mild or moderate in intensity.

In a relatively small number of patients, pneumonitis, MDS/AML and new primary malignancies have been observed. Evidence from across the development programme for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events. These are important potential risks for olaparib and are being kept under close surveillance.

Data from studies of olaparib in combination with various chemotherapy agents indicate an increase in bone marrow toxicity (anaemia, neutropenia, thrombocytopenia) greater than expected if the agents had been administered alone. The effects are generally transient but treatment delays are common and alternative administration schedules/toxicity management processes are currently being evaluated within some of these studies. When this type of toxicity has occurred it has been managed by routine clinical practice including dose delays, dose reductions, intermittent dosing and/or the use of supportive care measures, including G-CSF. Currently, all ongoing olaparib combination studies are being closely monitored for myelotoxicity. Results of a Phase II study in combination with carboplatin/paclitaxel (Study D0810C00041) showed that addition of olaparib to carboplatin AUC 4 + paclitaxel in the chemotherapy phase had a generally similar tolerability profile to carboplatin AUC 6 + paclitaxel. The regimen of olaparib capsules 200 mg bd for 10 days out of 21, with carboplatin AUC 4 + paclitaxel had an acceptable and manageable tolerability profile in patients with recurrent serous

ovarian cancer. Olaparib tolerability during the monotherapy maintenance phase was consistent with the previously known safety and tolerability profile.

In Study D0810C00039 and Study D081BC00004, olaparib 100 mg tablet bd in combination with weekly paclitaxel 80 mg/m2 was well tolerated, with no new unexpected safety findings. In both studies, the incidence of neutropenia was higher for the olaparib combination arm and this contributed to higher rates of dose modifications for patients on olaparib compared to placebo. In Study D081BC00004, there was also a higher incidence of anaemia on the olaparib + paclitaxel combination arm than on the placebo + paclitaxel arm and more dose interruptions, reductions and discontinuations (81).

A full description of most recent IP clinical data can be found in the current version of the olaparib IB

2.2.3 Combination Cediranib and Olaparib

NCI protocol 8348 included a phase I component that established the recommended phase II dosing (RP2D) of cediranib in combination with olaparib in the capsule formulation. This phase I enrolled a total of 28 patients (20 ovarian, 8 breast)(54).

At the highest dosing level of cediranib 30 mg daily (QD) and olaparib 400 mg BID, two DLTs were observed (grade 4 neutropenia and thrombocytopenia), and the RP2D was declared to be cediranib 30 mg QD and olaparib 200 mg BID64. Only one additional grade 4 adverse event (AE) (neutropenia) was observed. Fatigue (93%), diarrhea (86%), nausea (57%), and hypertension (45%) were the most commonly observed AEs, consistent with previously reported toxicities of cediranib and olaparib. Fatigue, which has been observed with both cediranib and olaparib in single-agent studies, may have been more prominent due to overlapping toxicity. Diarrhea was generally controllable with loperamide, although several patients required dose reduction. Hypertension, a well-documented toxicity of cediranib, was manageable with aggressive anti-hypertensive therapy; of note, only one patient required dose reduction for hypertension. Although all three grade 4 AEs observed were hematologic, in general, the combination was well-tolerated with primarily grade 1/2 hematologic toxicities.

Twenty-five patients (18 ovarian, 7 breast) from the phase 1 portion were evaluable for response by RECIST criteria, version 1.164. The two ovarian cancer patients not evaluable by RECIST 1.1 were followed by Gynecologic Cancer InterGroup (GCIG) CA125 criteria. The non-evaluable breast cancer patient experienced clinical progression within the first cycle of treatment and therefore did not undergo comparative imaging. There was one confirmed CR and seven confirmed PRs among the 18 evaluable ovarian patients, for an ORR of 44%. An additional three patients had SD for at least 24 weeks, for an overall clinical benefit rate of 61%. Both ovarian patients followed by CA125 had SD, with one patient having SD for ≥24 weeks. In the 11 evaluable ovarian patients with known BRCA mutation, there was one CR and four PRs, for an ORR of 45%. None of the breast cancer patients met RECIST 1.1 criteria for clinical response. Two patients had

SD for ≥24 weeks. The median PFS was 8.7 months for ovarian cancer patients and 3.7 months for breast cancer patients.

Dose escalation of cediranib in combination with olaparib in the tablet formulation has been completed in NCI protocol 8348 through a phase I-T component. Six doses of cediranib and olaparib tablets were explored (number of patients on each dose level in parentheses):

- Cediranib 20 mg daily / Olaparib 200 mg BID (3)
- Cediranib 20 mg daily / Olaparib 250 mg BID (3)
- Cediranib 20 mg daily / Olaparib 300 mg BID (6)
- Cediranib 30 mg daily / Olaparib 150 mg BID (3)
- Cediranib 30 mg daily / Olaparib 200 mg BID (6)
- Cediranib 30 mg daily / Olaparib 250 mg BID (3)

Three DLTs were observed across all patients enrolled to 8348 Phase 1-T; one DLT in the six patients on cediranib 30 mg/olaparib 200 mg, and two DLTs in the two patients on cediranib 30 mg/olaparib 250 mg. The RP2D was therefore concluded to be cediranib 20 mg daily and olaparib tablets 300 mg BID or cediranib 30 mg daily and olaparib tablets 200 mg BID. Six responses (CR or PR) were observed in the 24 patients on the study; these included one CR in the six patients on the cediranib 20 mg/olaparib 300 mg dosing and one CR and two PRs in the six patients on the cediranib 30 mg/olaparib 200 mg dosing. To preserve uniformity of cediranib dosing with prior clinical trial experience, the dose of cediranib 30 mg daily and olaparib tablet 200 mg BID will be further explored in this study.

2.3 Other Agents

Please reference the individual FDA package inserts for carboplatin, cisplatin, and etoposide for background information. Agents will be administered per standard of care guidelines in accordance with institutional standards and the FDA prescribing information.

2.4 Correlative Studies Background

2.4.1 Tumor PARP Immunohistochemistry

Based on pre-clinical analysis of lung tumors and cell lines, it's hypothesized that patients with elevated PARP1 protein expression by immunohistochemistry (IHC) will have greater susceptibility to PARP inhibitor therapy, and that patients whose tumors have high PARP1 expression will have superior outcome when treated with olaparib. In a previous study of lung cancer, the greatest in vitro activity of PARP inhibitors was observed in SCLC models and this was associated with significantly higher PARP1 protein levels in both pre-clinical models of SCLC and SCLC clinical specimens(3).

It is predicted that high PARP1 expression levels by IHC may be a biomarker of PARP inhibitor sensitivity in lung cancer. It is expected that those patients with elevated PARP1 protein levels will demonstrate a superior outcome when treated with olaparib. The

outcome data in patients with PARP1 H-scores above 200 (high PARP1) or below 200 (low PARP1) in the olaparib-treated patients will be compared. H-scores will be calculated based on the intensity of IHC staining (0-3) times the percentage of tumor cells staining positive (as previously described15). As there is not an established threshold for PARP1 positivity, an exploratory analysis looking at the association of PARP1 expression (H-score) as a continuous variable and PARP1 expression intensity as a categorical variable based (0, 1+, 2+, 3+) with relevant clinical endpoints (e.g., response, PFS, OS) will also be performed. As an alternative to IHC (depending on available tissue/profiling data), PARP1 levels could be assessed at the mRNA level, as correlation between protein and mRNA levels has previously been shown.

More recently, SLFN11 has emerged as an important predictive biomarker of response to PARP inhibition including with olaparib in SCLC models, with loss of SLFN11 conferring resistance to PARP inhibition (55, 56). In patient-derived xenografts, high SLFN11 (by H-score) was associated with response to PARP inhibition and treatment with PARP inhibitors resulted in a decrease in SLFN11 levels suggesting regulation of SLFN11 expression by PARP (56).

2.4.2 Plasma Angiome Analysis

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

Recently, a multiplex ELISA approach has identified several strong candidate predictors of benefit from bevacizumab(57-59). This approach was also used to identify IL-6 as a strong candidate predictive biomarker for anti-VEGF therapy in renal cell carcinoma. This marker was found to be a predictive marker in two independent phase III studies, each of which used a different VEGF inhibitor(10). Numerous other inflammatory mediators have been shown to regulate tumor angiogenesis and sensitivity to anti-VEGF therapy(60, 61). Tumor angiogenesis, inflammation, and anti-tumor immunity have highly interconnected biologies, a topic that has been extensively reviewed(62-64). However, to date, these factors have not been systematically interrogated in most anti-VEGF therapy trials. Analysis of the role of inflammation in mediating resistance to anti-VEGF therapy is now highly clinically relevant, particularly since most of these factors are now targetable in the clinic with agents either FDA approved or in clinical trials.

The application of multiplex ELISA approaches in clinical samples is rapidly evolving, having only recently shown positive results. Many of the analytes in the planned multiplex array were developed specifically for this use and have been carefully

optimized for performance in plasma and serum samples from cancer patients. The approach utilizes the Searchlight™ platform from Aushon BioSystems Incorporated. The specific panel design is depicted in Table 1 below. All antibody pairs have been validated to limit cross-reactivity and optimal dilutions were identified for every panel. Specific blocking buffers were identified, cross-reactivity of antibodies was tested and non-specific binding was minimized. Preliminary testing and plate validation were performed by independent laboratory groups. Freeze/thaw stability tests were done for all individual analytes. Lastly, assay performance across the different tissue types (citrated plasma, EDTA plasma and serum) was evaluated.

Table 1: Plasma-based marker identification

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

This approach is technically robust and readily adaptable to clinical practice. As this data will be derived from patients, even preliminary data may significantly improve understanding of how angiogenesis and tumor growth factors are regulated in cancer patients. Promising findings can be followed up in future clinical studies and in pre-clinical models. It is anticipated that through collection of blood based biomarkers, candidate markers of benefit that are specific for anti-angiogenic agents will be identified and validated and will offer multiple prognostic factors.

Baseline, post-1 cycle of therapy, post-1 cycle of maintenance therapy (or corollary time point for no maintenance cohort) and progression levels will be quantified and change from baseline will be determined for all analytes at the desired time points. Blood analytes will be correlated with PFS and/or OS.

2.4.3 Whole Exome Sequencing and Whole Transcriptome Sequencing

The Broad Institute has, to date, generated a total of over 2,500 x 1012 bases (2,500 Terabases) of sequence data using next-generation sequencing (NGS). The Broad Institute has substantial experience with whole exome sequencing (WES), and in fact invented one of the most commonly used approaches available today(65). The protocol involves generating tens of thousands of 120-mer oligonucleotides on solid arrays, cleaving them from the array and converting them into single-stranded, biotin-labeled

RNA "baits" to drive hybridization through high concentration. This protocol has been licensed to Agilent, and this method has now been used in more than 500 publications.

The sequencing platform of the Broad Institute boasts 50 Illumina HiSeq instruments and 10 MiSeqs, for an average capacity of 2.1 Terabytes (spanning 6192 flow cells) per day. The whole-exome panel includes: 18,557 genes (selected from RefSeq CDS) comprising 185,915 exons and 33 Mb of target. These targets are covered by 277,944 oligo "baits." A new exome-wide bait set is being adapted that allows more even sequence coverage per capture reaction; this innovation will allow the sequencing of clinical tumor samples to a sufficient overall mean coverage, while preserving the overall sensitivity and specificity of variant calling.

To perform WES, nucleic acid (DNA and RNA) will be obtained from circulating free DNA or tumor tissue using standard operating procedures in common use at the Broad Institute. For clinical tumor specimens, a "high-coverage" sequencing approach will be utilized, which should yield an average coverage of 150-200 fold; paired normal DNA will be sequenced to a depth of approximately 80-100-fold. WES data will be analyzed for base mutations, small insertions/deletions, and copy number alterations.

In parallel, the Broad Genomics Platform will perform whole transcriptome sequencing. The Broad Genomics Platform has extensive experience with whole transcriptome sequencing from both frozen and FFPE tumor samples. Regarding the latter, transcriptome capture is an alternative to traditional transcript enrichment methods (including polyA selection and ribosomal depletion) that is optimal for low-input and de¬graded samples including formalin-fixed paraffin-embedded (FFPE) tissues. The approach first prepares a stranded cDNA library from isolated RNA, then hybridizes the library to a set of DNA oligonucleotide probes to enrich the library for mRNA transcript fragments. Transcriptome Capture targets 21,415 genes, representing 98.3% of the RefSeq exome. In biological scenarios this assay has achieved expected results. For example, in one patient tumor at three time points, the third time point manifested robust KRAS amplification in the DNA that had concomitant over-expression of KRAS in the RNA from that same tumor.

WES of tumor tissue (as available) and tumor-derived circulating free DNA (cfDNA) from blood will be used to evaluate whether there are genomic alterations that may be associated with improved PFS with the combination of olaparib plus cediranib maintenance therapy or with standard therapy. The data gathered from comparisons of germline and tumor DNA will also permit single nucleotide polymorphism (SNP) profiling. SNP analysis will be performed to identify germline SNPs in angiogenesis gene and DNA repair genes associated with improved PFS.

2.4.4 Whole Exome Sequencing from Circulating Free DNA

Dr. Love and colleagues in concert with the Broad Institute initiatives under Dr. Garraway have demonstrated that accurate and powered WES of circulating tumor cells (CTCs) is both possible and likely useful clinically(66). This was first established in

experimental and analytical workflows for census-based sequencing of single CTCs and then validated in patients with metastatic prostate cancer. The approach is currently being validated in other tumor types including SCLC. This same approach is also being extended to the sequencing of tumor-derived cfDNA.

Blood sample collections will occur at baseline, after cycle 1, after cycle 2, after cycle 1 of maintenance therapy (or corollary time point in no maintenance cohort), cycle 3 day 1 of maintenance therapy, and at the time of progression. Each blood sample would be processed for CTCs, cfDNA, and germline DNA. The extraction of cfDNA and germline DNA will be performed from frozen aliquots of plasma and white blood cells, respectively. The yields and purities of cfDNA will be assessed prior to WES. It has been recently demonstrated that the yield and purity of cfDNA from a set of previously collected SCLC plasma samples is adequate for sequencing (25-30%) with variance in the quantity through the course of therapy. DNA samples will be subjected to the same WES analysis at the Broad Institute described in Section 2.4.3. In addition to evaluating genomic alterations in DNA extracted from blood, the findings will be compared to parallel sequencing analysis done on tissue biopsies from the same subjects to compare similarities and any potential differences. This analysis will help us to determine whether cfDNA sequencing may be a possible substitute for tissue-based sequencing which would be critical particularly in this tumor type given the difficulty in obtaining adequate tissue for molecular analysis. We will also evaluate quantitative changes in tumor-derived cfDNA through the course of therapy to determine correlation with tumor burden.

2.4.5 BROCA-HR

In order to respond to a PARP inhibitor, cancer cells need to be deficient in homologous repair (HR) mechanisms but also proficient in the alternative error prone non-homologous end joining (NHEJ) DNA repair pathway(67, 68). Loss of HR is not by itself sufficient for PARP inhibitor sensitivity, and an accurate predictor of PARP inhibitor responsiveness could require assessment of many components of both the HR and NHEJ pathways. A more efficient assay, which would not require a prior knowledge of the critical elements in these DNA repair pathways, would instead measure DNA repair capacity.

BROCA is a targeted capture and massively parallel sequencing assay that is capable of identify all classes of mutations including gene rearrangements(69, 70). Using BROCA, Walsh et al demonstrated that nearly one-fourth of women with ovarian carcinoma have germline loss of function mutations in at least 12 genes(69). Furthermore, most of these genes are in the BRCA-FA pathway. After BRCA1/2, the most common genes mutated in women with ovarian cancer are BRIP1 (FANCJ), RAD51D, RAD51C (FANCO), and PALB2 (FANCN)(69, 71). Pennington et al applied BROCA to detect somatic mutations in tumor DNA from 363 women with ovarian carcinoma. Combining germline and somatic mutations increased the fraction of cases identified with HRD to 31%, including 23% with germline and 9% with somatic mutations in FA/HR genes (and 1% with both somatic and germline mutations). The presence of either a germline or somatic FA/HR mutation is highly predictive of an improved primary response to platinum chemotherapy

(p<0.0005) and longer overall survival (p=.001)(72). Germline and somatic loss of function mutations were identified in all of the 13 FA/HR genes evaluated.

Dr. Swisher's laboratory has designed a new version of BROCA (BROCA-HR) that includes many additional DNA repair genes (75 total genes) as well as 3000 SNPs. Similar sequencing accuracy and sensitivity sequencing DNA is obtained from FFPE, fresh blood and flash frozen specimens. BROCA-HR includes genes that are targets of both somatic and germline mutations. The BROCA-HR includes genes that regulate HR or NHEJ that if mutated, could mediate resistance to PARP inhibitors such as TP53BP1(73-75). The BROCA design is flexible and can be altered to include any genes of research interest. The current design for BROCA-HR includes the following genes:

BROCA-HR gene list (n=75)

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

BROCA-HR analysis will be used to determine whether there are alterations in DNA repair genes that characterize a state of HR deficiency that is associated with improved PFS with olaparib plus cediranib combination maintenance therapy as compared with standard no maintenance therapy.

2.4.6 Circulating Tumor Cells for Cell Derived Xenograft Models

Participants enrolling to this trial will also be offered participation in a companion study from the NCI for blood collection to generate novel cell lines and cell-derived xenografts at the National Cancer Institute (NCI). This separate companion protocol (NCI 9846) will allow expeditious collection of samples that are essential to allow generation of patient-derived models and cell lines, which must be derived from fresh, viable tissue for further study of SCLC.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Histologically or cytologically confirmed diagnosis of extensive-stage small cell lung cancer with no prior systemic treatment.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with conventional techniques or as ≥10 mm (≥1 cm) with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.3 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of cediranib in combination with carboplatin/cisplatin plus etoposide or cediranib plus olaparib in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.4 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.5 Patients must have normal organ and marrow function within 28 days prior to administration of therapy as defined below:

– White blood cell count (WBC)	≥ 3 × 10^9/L
– No features suggestive of MDS/AML on peripheral blood smear	
– Absolute neutrophil count	≥1,500/mcL
– Platelets	≥100,000/mcL
– Hemoglobin	≥ 10 g/dL with no blood transfusion within 28 days of initiation of therapy.
– Total bilirubin	≤ 1.5 × institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤ 2.5 × institutional ULN, unless liver metastases are present and then ≤ 5 × institutional ULN is acceptable
– Creatinine clearance	≥ 50 mL/min
- Proteinuria	Urine protein:creatinine ratio (UPC) of ≤ 1 OR ≤ 2+ proteinuria on two consecutive urinalysis/dipstick tests taken no less than 1 week apart. Patients with 2+ proteinuria on dipstick must also have a UPC of ≤ 0.5 on 2 consecutive samples.

3.1.6 Ability to swallow and retain oral medication.

3.1.7 The effects of olaparib and cediranib on the developing human fetus are unknown. For this reason and because other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and male patients and their partners who are sexually active must agree to use two highly effective forms of contraception in combination (see olaparib IB page 161-162 for acceptable methods) for the duration of study participation and for 3 months after completion of olaparib and cediranib administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.8 Postmenopausal or evidence of non-pregnant status for women of childbearing potential as confirmed by a negative urine or serum pregnancy test within 7 days prior to the start of therapy. Postmenopausal status is defined as:

--age ≥60 years, or
--age <60 with any one or more of the conditions below:
--amenorrheic for ≥1 year in the absence of chemotherapy and/or hormonal treatments,
--luteinizing hormone and/or follicle stimulating hormone and/or estradiol levels in the post-menopausal range,
--radiation-induced oophorectomy with last menses >1 year ago,
--chemotherapy-induced menopause with >1 year interval since last menses,
--surgical sterilization (bilateral oophorectomy or hysterectomy).

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

3.1.10 Participants must have archival tumor tissue available for analysis (minimum 20 5 um slide) or be able to undergo a baseline fresh tumor tissue biopsy.

3.1.11 Adequately controlled blood pressure. (defined as systolic blood pressure [SBP] of ≤ 140mmHg and diastolic blood pressure [DBP] of ≤ 90mmHg) on maximum of three antihypertensive medications. Participants must have a blood pressure (BP) of ≤ 140/90 taken in the clinic or hospital setting by a medical professional within 2 weeks prior to starting on study. It is strongly recommended that participants who are on 3 antihypertensive medications be followed by a cardiologist or a primary care physician for management of BP while on study.

3.1.12 Adequately controlled thyroid function, with no symptoms of thyroid dysfunction. Patients can be on thyroid hormone replacement medication. Asymptomatic patients with elevated TSH with normal T4/T3 are allowed to enroll, and recommended to follow with routine thyroid function test.

3.2 Exclusion Criteria

3.2.1 Patients who have had major surgery or trauma within 28 days prior to entering the study. Patients must have recovered from any effects of any major surgery and surgical wound should have healed prior to starting treatment.

3.2.2 Patients who have had radiotherapy within 14 days prior to entering the study.

3.2.3 Patients with a non-healing wound, fracture, or ulcer.

3.2.4 Patients who have not recovered from adverse events due to prior anti-cancer therapy (i.e., have residual toxicities > CTCAE Grade 1 or baseline, with the exception of alopecia).

3.2.5 Patients who are receiving any other investigational agents.

3.2.6 Patients with symptomatic central nervous system (CNS) metastases or leptomeningeal carcinomatosis should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Exceptions include patients with previously-treated CNS metastases or those with asymptomatic, subcentimeter metastases, and have no requirement for steroids or anti-seizure medication for at least one week prior to study entry. Screening with CNS imaging studies (CT scan or MRI) is required.

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

3.2.8 Patients with a history of myelodysplastic syndrome (MDS).

3.2.9 Patients with a history of acute myeloid leukemia (AML), or patients with a history of any other primary malignancy within 3 years prior to initiation of treatment on this study. Exceptions include: patients with a history of malignancies (other than AML) that were treated curatively and have not recurred within 3 years prior to study entry; resected basal and squamous cell carcinomas of the skin; and completely resected carcinoma in situ of any type.

3.2.10 Patients with clinically significant gastrointestinal abnormalities including, but not limited to:

- Clinically significant signs and/or symptoms of bowel obstruction within 3 months prior to starting treatment.
- History of intra-abdominal abscess within 3 months prior to starting treatment.
- History of GI perforation within 6 months prior to starting treatment
- Evidence of abdominal fistula within 6 months prior to starting treatment. History of abdominal fistula will be considered eligible if the fistula was surgically repaired, and there has been no evidence of fistula for at least 6 months prior to starting treatment, and patient is deemed to be at low risk of recurrent fistula.

3.2.11 Patients with a history of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or insufficiently treated deep venous thrombosis (DVT) within the past 3 months. Note: Participants with recent DVT who have been treated with therapeutic anti-coagulants for at least 6 weeks are eligible, with the exception of participants being treated with warfarin, which is prohibited on this study. Other oral anti-coagulants may be allowed after discussion with overall PI, but short half-life low molecular weight heparins are strongly preferred.

3.2.12 Patients with evidence of active bleeding diathesis.

3.2.13 Patients with hemoptysis in excess of 2.5 mL within 6 weeks prior to the first dose of study medication.

3.2.14 Patients receiving any medications or substances that are potent inhibitors or inducers of CYP3A4 are ineligible. The required washout period for strong inhibitors is 2 weeks and at least one week for moderate inhibitors. The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 4 weeks for other agents, because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Details regarding concomitant medication administration are located in Section 5.3.

3.2.15 Patients requiring concomitant therapy with phenytoin, phenobarbital, carbamazepine, or valproic acid.

3.2.16 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. Specifically, patients with any of the following within 6 months prior to starting treatment are excluded:

- Acute myocardial infarction
- Unstable angina
- New York Heart Association functional classification of III or IV.
- Left ventricular ejection fraction (LVEF) < lower limit of normal (LLN) per institutional guidelines, or <55%
- Prior allogeneic bone marrow transplant or double umbilical cord blood transplantation
- Patients with active hepatitis (B or C)
- Patients with active pneumonitis

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

3.2.18 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with olaparib and cediranib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.19 Patients must be willing and able to check and record daily blood pressure readings if receiving cediranib.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

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

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 CTEP Registration Procedures

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

Registration requires the submission of:

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

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

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

4.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

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

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

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

An active CTEP-IAM user account is required to access all CTEP applications and, if applicable (*e.g.*, all Network trials), all Cancer Trials Support Unit (CTSU) applications and websites.

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

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

4.2 Site Registration

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites

using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 9974 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-MA036, and protocol # 9974.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 9974 Site Registration:

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

4.2.3 Submitting Regulatory Documents

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

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

4.2.4 Checking **Site** Registration Status

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

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

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

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

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

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

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

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

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

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

4.3.3 Patient Enrollment Instructions

n/a

4.3.4 OPEN/IWRS Questions?

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

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11 This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

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

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential

risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Bisphosphonate use is permitted. Participants receiving maintenance therapy may be permitted to have palliative radiation therapy on a case-by-case basis following discussion with the site investigator.

Patients will be randomized prior to initial therapy to receive cisplatin/carboplatin and etoposide alone, or cisplatin/carboplatin and etoposide in combination with cediranib. The decision to use cisplatin or carboplatin will be left to the treating investigator; however the decision of which platinum agent to use should be made prior to the initial randomization. Randomization will occur in a 2:1 ratio such that two-thirds of the participants will be randomized to receive cisplatin/carboplatin and etoposide alone.

Following completion of four cycles of initial therapy, participants who were randomized to receive cisplatin/carboplatin and etoposide alone and have stable disease, partial, or a complete response will be randomized equally to receive either no maintenance therapy or maintenance therapy with cediranib plus olaparib. Participants who received cediranib during the initial therapy phase will be directly assigned to receive maintenance therapy with cediranib and olaparib following initial therapy.

Participants who do not receive maintenance therapy will be eligible to crossover to receive treatment with cediranib plus olaparib upon disease progression at the treating investigator's discretion. Because of the extremely limited efficacy of 2nd line regimens for SCLC, the 1st recommendation by NCCN guidelines is participation in a clinical trial. Response rates following disease progression after initial therapy for SCLC vary between 0-20% (i.e. 20% RR to topotecan for chemotherapy-sensitive patients, but < 5% RR for those who are chemotherapy-resistant) with PFS to 2nd line therapy varying between 1-4 months. Cediranib in the maintenance setting in a small trial conducted by Heymach and colleagues had an improved PFS compared to historical controls and the combination of cediranib + olaparib in other tumor types has been demonstrated to be synergistic in improving PFS (Liu et al., 2013). Overall, given the preclinical rationale for the combination for efficacy (as detailed in the protocol) as well as clinical data from other tumor types, we feel this combination is a reasonable strategy to offer patients with progression on 1st line therapy in the context of this clinical trial (where response and outcomes may be systematically evaluated).

Randomization to maintenance/no maintenance therapy should occur within two weeks of completion of initial therapy and follow-up radiation, which will include consolidation thoracic radiation ± prophylactic cranial irradiation as appropriate. If both thoracic and cranial irradiation are performed, they should be performed concurrently. Maintenance therapy should begin when radiation-associated toxicity has resolved to CTCAE ≤ grade 1 or baseline (with the exception of alopecia). Treatment should start no sooner than 3 weeks and no later than 6 weeks after completion of radiation therapy. A new baseline scan should be obtained at the start of maintenance therapy.

Table 2: Regimen Description – Initial Therapy Phase						
Agent	***Premedications; Precautions***	***Dose****	***Route***	***Schedule***	***Cycle Length***	***Number of Cycles***
Cediranib§	Patients should fast for 2 hours before and 1 hour after each dose.	20 mg	Oral	Daily	21 days (3 weeks)	4
Cisplatin∂	As per institutional standards	75 mg/m^2	IV	Day 1		
Carboplatin∂	As per institutional standards	AUC 6	IV	Day 1		
Etoposide	As per institutional standards	100 mg/m^2	IV	Days 1, 2, 3		
**: Body Surface Area (BSA) to be calculated per institutional standards* *§: Cediranib will only be given to patients randomized to the cediranib treatment arm* *∂: Either cisplatin or carboplatin may be given at the treating investigator's discretion*						

Table 3: Regimen Description – Maintenance Phase					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Cediranib	Patients should fast for 2 hours before and 1 hour after each dose	30 mg	Oral	Daily	28 days (4 weeks)
Olaparib	Tablets can be taken by mouth with a light meal/snack	200 mg	Oral	Twice daily	

Participants will be requested to maintain a study medication diary that will indicate each dose of oral medication taken to illustrate treatment compliance. The medication diary should be returned to appropriate research staff for review at the end of each treatment cycle.

5.1.1 Cediranib

Cediranib is available as a beige film-coated tablet containing 20 mg or 15 mg of cediranib. Patients can be administered cediranib study treatment tablets orally at a dose of 30 mg or 20 mg once daily (od). Subjects who are randomized to receive cediranib during the initial therapy phase will take cediranib at the dose of 20 mg by mouth daily each day of the 21 day cycle for four cycles. Following the initial therapy phase, patients receiving cediranib plus olaparib as maintenance therapy will receive cediranib at 30 mg (2 x 15mg tablets) by mouth daily each day of the 28 day maintenance cycles. Cediranib will be given each morning on an empty stomach, patients should be instructed to fast for a minimum of two hours before each dose and continue to fast for one hour after each dose. Cediranib should be taken with a glass of water. Doses should be taken approximately 24 hours apart. A missed dose may be taken up to two hours after the regularly scheduled dosing time. Doses outside of this time frame should be considered missed and should not be taken. Patients should be instructed to swallow cediranib whole; it should not be chewed, crushed, or dissolved. A vomited dose should not be retaken; instead participants should be instructed to continue with their next regularly scheduled dose as clinically appropriate.

One x 20 mg and 1 x 15 mg tablets is used to manage dose reductions

Please see Section 5.2 for concomitant medication and supportive care guidelines.

5.1.2 Olaparib

Olaparib is available as a film-coated tablet containing 150 mg or 100 mg of olaparib. Patients can be administered olaparib study treatment tablets orally at a dose of 200 mg twice daily (bd). Patients randomized to receive olaparib plus cediranib as maintenance therapy will take olaparib at 200 mg (2 x 100mg tablets) by mouth twice daily each day of the 28 day maintenance cycle. Patients should be instructed that they may take olaparib with a light meal or snack. Doses should be taken approximately 12 hours apart. A missed dose may be taken up to two hours after the regularly scheduled dosing time. Doses outside of this time frame should be considered missed and should not be taken. Patients should be instructed to swallow olaparib whole; it should not be chewed, crushed, or dissolved. A vomited dose should not be retaken; instead participants should be instructed to continue with their next regularly scheduled dose as clinically appropriate. As cediranib must be taken on an empty stomach, for participants randomized to combination therapy, they will be advised to take the Cediranib as soon as they wake up (fasting) and then 1 hour afterwards take the olaparib with breakfast or a snack. Alternatively, if this is a difficult schedule, taking olaparib with breakfast/light snack followed by cediranib 2 hours later is also permitted to maintain fasting dosing of cediranib. At night (12 hours after olaparib morning dose) they would take the olaparib with a snack or light meal.

One x 150 mg and 1 x 100 mg tablets is used to manage dose reductions.

Participants should be instructed to avoid consuming grapefruit and grapefruit juice while on study. Please see Section 5.2 for concomitant medication and supportive care guidelines.

5.1.3 Cisplatin

Either cisplatin or carboplatin will be given to all participants during the initial therapy phase on day 1 of each 21 day cycle for four cycles. The decision to use cisplatin or carboplatin will be left to the treating investigator. Participants who receive cisplatin will receive it at a dose of 75 mg/m2 IV in 0.9% NaCl over 60 minutes. BSA calculations and recalculation of the dose at the start of each subsequent cycle due to changes in the participant's weight should be performed per institutional standards. Cisplatin will be given as per institutional policies and the FDA prescribing information.

Hypersensitivity reactions have been reported in patients who have received cisplatin. The reactions typically consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated. Patients receiving

cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

5.1.4 Carboplatin

Either cisplatin or carboplatin will be given to all participants during the initial therapy phase on day 1 of each 21 day cycle for four cycles. The decision to use cisplatin or carboplatin will be left to the treating investigator. Participants who receive carboplatin will receive it IV at a dose of AUC 6 in 0.9% NaCl over 60 minutes. All dosing calculations should be performed per institutional standards. Carboplatin will be given as per institutional policies and the FDA prescribing information.

Hypersensitivity to carboplatin has been reported in 2 percent of patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, i.e., rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of post-marketing surveillance. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy. Please see FDA prescribing information.

5.1.5 Etoposide

Etoposide will be given to all participants during the initial therapy phase on days 1, 2, and 3 of each 21 day cycle for four cycles. Participants will receive etoposide at a dose of 100 mg/m2 IV in 0.9% NaCl over 60 minutes. BSA calculations and recalculation of the dose due to changes in the participant's weight should be performed per institutional standards. Etoposide will be given as per institutional policies and the FDA prescribing information.

Anaphylactic-type reactions characterized by chills, rigors, tachycardia, bronchospasm, dyspnea, diaphoresis, fever, pruritus, hypertension or hypotension, loss of consciousness, nausea, and vomiting have been reported to occur in approximately 3 percent of all patients treated with etoposide. Facial flushing was reported in 2 percent and skin rashes in 3 percent of patients receiving etoposide. These reactions have usually responded promptly to the cessation of the infusion and administration of vasopressor agents, corticosteroids, antihistamines, or volume expanders as appropriate; however, the reactions can be fatal. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the initial infusion.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of cediranib and olaparib with other concomitantly administered drugs, the case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Patient Drug Information Handout and Wallet Cards

(APPENDIX B and APPENDIX C) should be provided to patients if available and applicable.

All participants receiving protocol therapy may receive antiemetics, antidiarrheals, and blood product transfusion support as necessary and per local guidelines. Use of granulocyte colony stimulating factors (G-CSF) will be at the treating investigator's discretion. Use of other concomitant medications are allowed with the exception of the medications detailed in the below Sections **5.2.2, 5.2.3, 5.2.4, 5.2.5,** and **5.2.6**. Specific toxicity management guidelines are located in Section **6**.

Cediranib may impair wound healing. For this reason, cediranib should be held for two weeks prior to any surgical procedures and may be restarted when the surgical wound is healed.

5.2.1 Blood Pressure Monitoring with Cediranib

Frequent blood pressure monitoring is important in patients receiving cediranib. Clinical trials of cediranib have demonstrated 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. Anti-hypertensives should be utilized as needed to control blood pressure, please see APPENDIX G for suggested antihypertensive medications.
Blood pressure monitoring cuffs are provided by Astra Zeneca and should be ordered once an eligible subject has been registered within the OPEN IWRS. The Blood Pressure Cuff Request Form can be found on the CTSU portal.

All patients receiving cediranib will be asked to record twice daily blood pressure readings during the first 9 weeks of cediranib therapy (APPENDIX H). If anti-hypertensive management is required, twice daily blood pressure monitoring must continue until a stable anti-hypertensive regimen has been established, even if this requires more than 9 weeks of monitoring. Following 9 weeks or once a stable anti-hypertensive regimen has been achieved; blood pressure monitoring may be reduced to once daily. Twice daily monitoring should be re-implemented after any cediranib hold/dosing delay for ≥ two weeks or until the patient is re-established on a stable anti-hypertensive regimen, whichever takes longer.

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 study physician as soon as possible. Patients should seek immediate medical advice if their blood pressure exceeds 180 mmHg (systolic) or 105 mmHg (diastolic) at any time and should also be encouraged to contact their study 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 Cediranib Concomitant Medication Guidelines

Cediranib (AZD2171) is primarily metabolized by flavin-containing monooxygenase enzymes (FMO1 and FMO3) and UGT1A4. It is not a substrate of CYP450 enzymes. In vitro studies suggest that cediranib is a substrate for P-glycoprotein (Pgp), but not breast cancer resistance protein (BCRP). Since clinically relevant induction or inhibition of FMO enzymes is uncommon, use caution in patients taking concomitant medications that are strong inhibitors (e.g. ketoconazole) or strong inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's Wort) of UGT1A4 or Pgp in particular. If chronic concomitant administration of strong inducers or inhibitors is unavoidable, consult the principal investigator before proceeding with screening. Ideally, the use of strong inhibitors of UGT1A4 should be avoided at least one week prior to administration of cediranib.

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

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

Cediranib is approximately 95 percent bound to human plasma proteins, with human serum albumin and α1-acid glycoprotein accounting for most of this binding. Use caution in patients taking concomitant medications with narrow therapeutic ranges that are also highly protein-bound.

Patients receiving cediranib are at increased risk of bleeding and hemorrhage. For this reason, warfarin use is prohibited on trial. Low-molecular weight heparin is allowed but should be used with caution. Participants taking low-molecular weight heparins should be closely monitored for signs and symptoms of bleeding.

5.2.3 Olaparib Concomitant Medication Guidelines

Contraception
Female patients of child bearing potential and male patients with partners of child bearing potential, who are sexually active, must agree to the use of two highly effective forms of contraception. This should be started from the signing of the informed consent and continue throughout period of taking study treatment and for 1 month (female patients)/3 months (male patients) after last dose of study drug. Acceptable non-hormonal and hormonal birth control methods may be found in the Olaparib IB.

Use of Natural/Herbal Products
The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the case

report form (CRF).

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

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

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

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

The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.
Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Examples of substrates include:

- *CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine*
- *CYP1A2 – duloxetine, melatonin*
- *CYP2B6 – bupropion, efavirenz*
- *CYP2C9 – warfarin*
- *CYP2C19 - lansoprazole, omeprazole, S-mephenytoin*
- *P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine*
- *OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan*
    - The required washout period prior to starting study treatments is 2 weeks for strong inhibitors listed above, and at least 1 week for moderate inhibitors listed above.
    - The required washout period prior to starting study treatments is 5 weeks for enzalutamide or phenobarbital and 4 weeks for other agents.

Based on in vitro data and clinical exposure data, animal in vivo data, and clinical exposure data, olaparib is primarily metabolized vis CYP3A4/5 (direct inhibitor of CYP3A in vitro). Therefore, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.

While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug

interactions:

Ketoconazole, itraconazole, ritonavir, idinavir, saquinavir, telithromycin, clarithromycin and nelfinavir

For patients taking any of the above, the required wash-out period prior to starting olaparib is one week. In addition, to avoid potential reductions in exposure due to drug interactions and therefore a potential reduction in efficacy, the following CYP3A4 inducers should be avoided:

Phenytoin, rifampicin, rifapentine, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (Hypericum perforatum)

For patients taking any of the above, the required wash-out periods prior to starting olaparib are 3 weeks (5 weeks for phenobarbitone).

After randomization if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the investigator must contact the Overall Principal Investigator. A decision to allow the patient to continue in the study will be made on a case-by-case basis. Additionally please refer to APPENDIX D.

Anti-emetics/Anti-diarrheals

If a patient develops nausea, vomiting and / or diarrhea, then these symptoms should be reported as AEs (see section 7) and appropriate treatment of the event given.

Anticoagulant Therapy

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

Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is

stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

Subsequent therapies for cancer

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

Medications that may NOT be administered with Olaparib

- No other immunotherapy, hormonal therapy or other novel agent is to be permitted while the patient is receiving study medication.

It is not recommended to consume grapefruit juice while on olaparib therapy.

5.2.4 Cisplatin Concomitant Medication Guidelines

Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy. Participants should be monitored closely and dosages adjusted accordingly. See FDA prescribing information.

5.2.5 Carboplatin Concomitant Medication Guidelines

The renal effects of nephrotoxic compounds may be potentiated by carboplatin. See FDA prescribing information.

5.2.6 Etoposide Concomitant Medication Guidelines

Caution should be exercised when administering etoposide with drugs that are known to inhibit phosphatase activities (e.g., levamisole hydrochloride). See FDA prescribing information. Concomitant use of antiepileptic medications including phenytoin, phenobarbital, carbamazepine, and valproic acid is associated with increased etoposide clearance and reduced efficacy of etoposide. For this reason, concomitant use of phenytoin, phenobarbital, carbamazepine, and valproic acid is prohibited during the initial therapy phase of the study.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s) or progressive disease, treatment will consist of 4 cycles of chemotherapy at minimum. For those randomized to the arm using cediranib or randomized to maintenance olaparib + cediranib, treatment on maintenance olaparib + cediranib will continue indefinitely until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent
- Bone marrow findings consistent with MDS and/or acute myeloid leukemia.

Participants who were randomized to receive no maintenance therapy may crossover to receive cediranib plus olaparib therapy upon disease progression at the treating investigator's discretion. If crossover occurs, treatment with olaparib + cediranib will continue indefinitely as above until one of the criteria note above applies. The first re-assessment after initiating crossover therapy will happen at 6 weeks after starting therapy.

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

5.4 Duration of Follow Up

Participants will be followed until death after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.

6. DOSING DELAYS/DOSE MODIFICATIONS

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

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

6.1 Dose Modification Guidelines

The dose levels and the general approach to dose modifications are shown below. AEs should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the CRFs.

Dose reductions will be based on the offending medication(s). In the event the treating investigator feels all medications are responsible for the toxicity, all medications can be reduced. Cediranib and olaparib dose modifications should be made according to the schedules outlined in **Table 4** and **Table 5**. Dose reductions of cisplatin, carboplatin, and etoposide should be made according to standard of care guidelines. Participants undergoing dose reductions for toxicities may not be re-escalated to a prior dose.

Participants who do not tolerate initial cisplatin treatment despite maximal supportive care may be changed to receive carboplatin at the treating investigator's discretion for the remainder of the initial therapy cycles. Similarly, participants who do not tolerate initial carboplatin treatment despite maximal supportive care may be changed to receive cisplatin at the treating investigator's discretion for the remainder of the initial therapy cycles. Participants may receive a maximum of four cycles of platinum therapy during the initial therapy period.

In rare circumstances, patients experiencing ongoing clinical benefit but who develop one of the toxicities listed below related to one of the IPs that prevents them to continue to take this IP, may be allowed to continue on the unrelated drug if in the opinion of the treating investigator the risk benefit remains favorable and only after discussion with the Principal Investigator.

AEs requiring cediranib to be discontinued:

- GI perforation
- Arterial Thromboembolic Event
- PRES
- Severe hemorrhage

- Severe persistent hypertension despite maximal anti-hypertensive treatment

AEs requiring olaparib to be discontinued:

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

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

Table 4: Cediranib Dose Modifications	
Original Cediranib Dose	**Cediranib Dose Reduction**
20 mg daily	15 mg daily
30 mg daily	1st Reduction: 20 mg daily
	2nd Reduction: 15 mg daily
Dose reductions below 15 mg daily will not be allowed, if a participant requires reduction below 15 mg daily they should be discontinued from cediranib therapy	

Table 5: Olaparib Dose Modifications	
Original Olaparib Dose	**Olaparib Dose Reduction**
200 mg twice daily	1st Reduction: 150 mg twice daily
	2nd Reduction: 100 mg twice daily
Dose reductions below 100 mg twice daily will not be allowed, if a participant requires reduction below 100 mg twice daily they should be discontinued from olaparib therapy	

6.2 Toxicity Management Guidelines

Management of hypertension (associated with cediranib) and diarrhea (associated with cediranib and/or olaparib is of particular concern. All participants will be asked to record twice-daily blood pressure measurements as well as log any diarrhea events in patient diaries . Guidelines for management are as per the tables below. Patient information regarding diarrhea management in also in appendix I.

6.2.1 Initial Therapy Phase

Dose delays and modifications of cisplatin or carboplatin and etoposide should follow institutional standards (namely, participants must meet re-treatment criteria prior to re-initiation of therapy and may be dose-reduced per institutional standards). However, if dosing of

chemotherapy that occurs concurrently with cediranib is held, then that day's dosing of cediranib should also be held. If dose –delay of chemotherapy for hematologic or other laboratory toxicity results in a > 3 week delay in therapy, protocol therapy should be discontinued. Exceptions to this may be reviewed on a case-by-case basis with the Overall Principal Investigator.

Participants receiving cediranib during the initial therapy phase should also meet treatment guidelines relating to cediranib therapy as outlined in **Table 6**, **Table 8**, **Table 9**, **Table 10**, **Table 11**, **Table 12**, **Table 13**, **Table 14, and Table 15**.

6.2.2 Maintenance Phase

Study treatment may be held for a maximum of 21 days to allow recovery from toxicity associated with treatment during the maintenance phase of therapy. Participants requiring longer delays should be discontinued from protocol therapy. Exceptions are possible for participants who are deriving clinical benefit in the opinion of the treating investigator after discussion with the overall principal investigator.

6.2.3 Cediranib Toxicity Management

6.2.3.1 Fatigue

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

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

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

6.2.3.2 Fistula

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

6.2.3.3 Arterial thromboembolism

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

events. Cediranib should be permanently discontinued in patients who develop an arterial thromboembolic event.

6.2.3.4 Venous thromboembolism

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

6.2.3.5 Wound healing

Treatment with cediranib should be stopped at least 2 weeks prior to scheduled surgery. The decision to resume cediranib therapy after surgery should be based on clinical judgment of adequate wound healing. In patients who experience wound healing complications during therapy, treatment with cediranib should be interrupted until the wound is fully healed. No formal studies of the effect of cediranib on wound healing have been conducted.

6.2.3.6 Elderly

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

6.2.3.7 Mild/moderate renally impaired patients

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

6.2.3.8 Decreased weight

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

6.2.4 Olaparib Toxicity Management

6.2.4.1 Pulmonary symptoms

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

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

6.2.4.2 Nausea and vomiting

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

No routine prophylactic anti-emetic treatment is required at the start of treatment with the IPs, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Taking olaparib tablets with food may help alleviate symptoms of nausea and vomiting.

6.2.4.3 Renal impairment

Olaparib has not been studied in patients with severe renal impairment (CrCL ≤30 mL/minutes) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

6.2.5 Interruptions for intercurrent non-toxicity related events

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

Both IPs should be stopped at least 2 weeks prior to planned surgery. After surgery both IPs can be restarted when the wound has healed. No stoppage of IPs is required for any needle biopsy procedure.

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

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

6.2.6 Non-Hematologic Toxicities and Management

Cediranib should be discontinued should any of the following AEs occur: GI perforation; arterial thromboembolic events; PRES (radiologically confirmed); severe or medically

significant hemorrhage and severe persistent hypertension despite maximal anti-hypertensive treatment.

Dose modifications for other non-hematologic events while on cediranib and/or olaparib should be managed according to Table 6.

Table 6: Management of Non-Hematologic Adverse Events Not Otherwise Specified (Related to Cediranib and/or Olaparib)	
Non-Hematologic CTCAE Event Grade	**Management Guidelines**
Grade 1; ***or*** any AE that resolves promptly with supportive care	Maintain dose level.
Grade 2 non-hematologic AE or grade 3 fatigue considered at least possibly related to study treatment that persists despite maximal supportive care.* Exceptions include: • Hypertension or other AEs with specific management instructions outlined in the tables below. • Non-clinically significant, asymptomatic, or easily correctable laboratory abnormalities. • Grade 3 fatigue that does not persist	Hold study drug(s) for up to 21 days until toxicity resolves to ≤ grade 1 or baseline. Treatment may be restarted at investigator discretion at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.2. Recurrence of Grade 3 or 4 toxicity would require dose reduction of both IPs. Patients whose toxicity has not resolved after 21 days will be removed from study. • At the discretion of the investigator, one IP may be held or dose modified or discontinued independently if the observed toxicity is attributed to only one of the drugs, while the patient continued to receive the second drug not associated with the observed toxicity. The time a given drug is held should not exceed 3 weeks. • Patients who are at the lowest reduced dose level may have their drug resumed at that dose level after discussion with the Principal Investigator if evidence of clinical benefit.
Grade 3 or 4 non-hematologic AE related to	Remove patient from protocol-specified

Table 6: Management of Non-Hematologic Adverse Events Not Otherwise Specified (Related to Cediranib and/or Olaparib)	
Non-Hematologic CTCAE Event Grade	**Management Guidelines**
cediranib and olaparib combination that does not resolve to Grade 0-2 within 3 weeks despite maximum supportive care after treating patient at the lowest reduced dose level Exceptions include: • Hypertension or other AEs with specific management instructions outlined in the tables below. • Non-clinically significant, asymptomatic, or easily correctable laboratory abnormalities.	treatment.
**: For thromboembolic events, treatment may be resumed at the discretion of the treating investigator once patient is asymptomatic.*	

6.2.7 Hematologic Toxicities and Management

6.2.7.1 Management of neutropenia and thrombocytopenia

Neutropenia and thrombocytopenia are recognized common adverse drug reactions reported for both olaparib and cediranib.

6.2.7.2 Management of anemia

Anemia is a common adverse drug reaction related to olaparib. Cediranib is not reported to increase the risk of anemia.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. Any subsequently required dose interruptions, related to development of anemia, or coexistent with newly developed neutropenia, and/or thrombocytopenia, will require olaparib dose reductions to 150 mg twice daily as a first step and to 100 mg twice daily as a second step.

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

6.2.7.3 Use of hematopoietic agents

Use iron supplements, and/or transfusions as clinically indicated for management of anemia. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended. They do not alleviate fatigue or increase energy. They should not be used in patients with

uncontrolled hypertension. The package inserts should be consulted.

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

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

6.2.7.4 Dose modifications for hematologic toxicity

Patients who have IPs held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery; these data should be recorded in eCRF as extra laboratory examinations. If counts do not improve to CTCAE Grade 1 or better despite drug cessation for 3 weeks, patients should be referred to a hematologist for further assessment. A bone marrow analysis should be considered per hematology assessment.

For AEs that are unrelated to the study drug, study drug may be withheld for up to 3 weeks at the discretion of the treating Investigator.

6.2.7.5 Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

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

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

Table 7: Management of Hematologic Adverse Events during Maintenance Therapy

Hematologic Event	Management Guidelines
Absolute neutrophil count ≥ 1000/mcL **AND** Platelets ≥ 100,000/mcL	**Olaparib dose**: Investigator judgement to continue treatment or allow dose interruption; dose interruptions should be for a maximum of

Table 7: Management of Hematologic Adverse Events during Maintenance Therapy	
Hematologic Event	**Management Guidelines**
	3 weeks; appropriate supportive treatment and causality investigation. **Cediranib dose**: Investigator judgement to continue treatment or allow dose interruption; dose interruptions should be for a maximum of 3 weeks; appropriate supportive treatment and causality investigation
Absolute neutrophil count < 1000/mcL **OR** Platelets <100,000/mcL	**Olaparib dose:** Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 3 weeks. Upon recovery, olaparib dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one or both IPs **Cediranib dose**: Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 3 weeks. Upon recovery, cediranib dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one or both IPs
Hb < 10 but ≥ 8 g/dL	**Olaparib dose**: Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib or interrupt dose for a maximum of 3 weeks. If repeat Hb <10 but ≥8 g/dL, dose interrupt until Hb ≥10 g/dL for maximum of 3 weeks and upon recovery dose reduce to 150 mg bd as a first step and to 100 mg bd as a second step **Cediranib dose**: No change
Hb < 8 g/d	**Olaparib dose**: Give appropriate supportive treatment and investigate causality. Interrupt olaparib until improved to Hb ≥10 g/dL. Upon recovery dose reduce olaparib to 150 mg bd **Cediranib dose**: No change

Table 8: Management of Hypertension (Associated with Cediranib)		
CTCAE Event Grade	**Blood Pressure Monitoring**	**Management Guidelines**
See APPENDIX G for suggested antihypertensive medications by class.		

Table 8: Management of Hypertension (Associated with Cediranib)		
CTCAE Event Grade	**Blood Pressure Monitoring**	**Management Guidelines**
Abbreviations: Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARB), selective beta blockers (BB), Dihydropyridine calcium channel blockers (DHP-CCP) All participants will be given blood-pressure monitors and asked to take their blood pressure twice-daily at home and record in a log. Any blood pressure measurement over 140/90 should prompt a call to the treating team so that expeditious blood pressure management can occur. Patient BP will also be measured during routine study visits to ensure that BP guidelines are being correctly followed. Increase in BP should be treated promptly with standard antihypertensive therapy, ensuring that the maximum recommended dose and number of antihypertensive medicinal products is reached before considering cediranib dose adjustment. If patients require a delay of >3 weeks for management of hypertension, discontinuation of cediranib therapy may be considered after discussion with the Overall Principal Investigator. In case of persistent or severe hypertension, despite the optimal use of antihypertensive medicinal products and cediranib dose reduction, cediranib should be permanently discontinued. Patients may have up to 4 drugs for management of hypertension prior to any dose reduction in cediranib Only doses of cediranib will be modified for hypertension; olaparib doses will not be reduced unless other toxicities are experienced. Please note: patients may have baseline hypertension meeting CTCAE grading criteria on study entry provided this is adequately controlled on a maximum of 3 antihypertensive medications. Should patients require increase in dosing of BP medication or increased number of medications, they should then be noted to have hypertension related to study drug, with grading as per CTCAE v5.0 criteria. Patients already taking antihypertensive therapy at baseline or those aged 75 years or older are at a higher risk of having elevated BP or may require more than one medicinal product or more intensive therapy. Pre-existing cardiovascular risks should be assessed and managed, and pre-existing hypertension should be adequately controlled before starting treatment with cediranib Baseline grade of hypertension should also be recorded in the patient's record. Should patients require increase in dosing of BP medication or increased number of medications, they should then be noted to have hypertension related to study drug, with grading as per CTCAE criteria. **Note:** Stopping or reducing the dose of cediranib is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly		
Grade 1	Continue standard BP	

Table 8: Management of Hypertension (Associated with Cediranib)		
CTCAE Event Grade	**Blood Pressure Monitoring**	**Management Guidelines**
	monitoring per treating MD and confirm resolution of BP <140/90 mmHg or baseline within 24 hours.	Maintain study drug dosing unless hold is otherwise clinically indicated. Consider early initiation of BP medication for BP > 140/90 mmHg that is confirmed on a second reading. Cediranib can cause rapid escalation in BP, and early initiation of BP management can reduce likelihood of HTN-related complications.
Grade 2	Increase frequency of monitoring until stabilized to BP <140/90 mmHg,	Maintain study drug dosing unless hold is otherwise clinically indicated. Initiate BP medication for first line treatment. *Suggestions:* ACE-inhibitor. Escalate dose of medication in step-wise fashion until BP is controlled or at a maximum dose. If BP is not controlled to < 140/90 mmHg with one drug regimen, then add a second agent. Consider renal consult.
Grade 3	Increase frequency of monitoring until stabilized to BP < 140/90 mmHg.	Do not hold cediranib unless BP is not decreased to less than 150/100 mmHg 48 hours after multi-drug therapy is instituted or if clinical symptoms worsen

Table 8: Management of Hypertension (Associated with Cediranib)		
CTCAE Event Grade	**Blood Pressure Monitoring**	**Management Guidelines**
		(e.g. headache). Maximize 2 drug regimen. *Suggestions:* ACE-inhibitor plus BB Escalate doses of existing medication until BP is controlled or at a maximum dose. If BP is not controlled to < 140/90 mmHg with two drug regimen, then add a third agent. Additional anti-hypertensive drugs, up to a total of 4, may be maximized for blood pressure control. If BP is not controlled to less than 150/100 mmHg with maximal therapy or if clinical symptoms worsen, then hold cediranib (up to 14 days) until maximum effect of the anti-hypertensive agents is achieved. If BP is reduced to < 140/90 within 14 days, cediranib may be resumed at the prior dose level. Consider consult with a blood pressure management specialist if greater than 3 drugs are required for BP control.
Grade 4	Intensive BP monitoring (hospitalization if necessary)	Hold cediranib. Initiate treatment. Hospitalize patient for ICU management, IV therapy as necessary. If BP is reduced to less than 140/90 within 14 days, cediranib

Table 8: Management of Hypertension (Associated with Cediranib)		
CTCAE Event Grade	**Blood Pressure Monitoring**	**Management Guidelines**
		may be resumed at a reduced dose after discussion with the Overall Principal Investigator.

Table 9: Management of Diarrhea (Associated with Cediranib and/or Olaparib or Etoposide)	
Non-Hematologic CTCAE Event Grade	**Management Guidelines**
Grade 1 or 2 (lasting ≤ 24 hours)	Maintain study drug dosing unless hold is otherwise clinically indicated. Patients can take loperamide per standard practice (guidelines in Appendix I) and continue to take loperamide until patients are free from diarrhea for at least 12 hours. Patients should also be counseled to start a bananas, rice, applesauce, toast (BRAT) diet.
Grade 1 or 2 (lasting ≥ 24 hours)	If diarrhea persists despite 24 hours of loperamide treatment, hold study medication for a maximum of 14 days, continue treatment with antidiarrheals, and maintain hydration. Study medication may be resumed at the same dose once patients have returned to baseline or have been free from diarrhea for 12 hours.
Persistent Grade 2, or Grade 3 or 4	Hold study drug(s) for up to 14 days until diarrhea resolves to ≤ grade 1 or baseline. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.2. Patients whose toxicity has not resolved after 14 days will be removed from study.
Diarrhea is often observed with cediranib. Diarrhea usually starts early (within the first 4 weeks of treatment), however, it can occur at any time during treatment. Management of diarrhea should start at the first sign of diarrhea. Loperamide and advice on how to manage diarrhea should be readily available to patients from the start of cediranib treatment so that they can be applied at first episode of diarrhea. Active and early management of diarrhea is recommended even with Grade 1 diarrhea.	

Table 10: Management of Proteinuria (Associated with Cediranib)	
Proteinuria if following by U/A	**Management Guidelines**
Greater than 2+ on urine dipstick or U/A **AND** Creatinine ≤ 1.5 × institutional ULN	Perform urine protein: creatinine ratio (UPC). Maintain study drug dosing unless hold is otherwise clinically indicated. See below management of UPC results.
Greater than 2+ on urine dipstick or U/A **AND** Creatinine > 1.5 × institutional ULN	Hold cediranib until results of UPC are known. See below management of UPC results.
Based on results of the UPC*:	
UPC ≤ 1	Continue routine monitoring prior to each cycle. Continue study drug dosing at planned dose.
UPC > 1 and ≤ 3.5 **AND** Creatinine ≤ 1.5 × institutional ULN	Perform UPC prior to each cycle. Continue study drug dosing at planned dose.
UPC > 3.5 OR Creatinine > 1.5 × institutional ULN	Perform UPC prior to each cycle. Hold cediranib for up to 7 days and repeat UPC and creatinine assessment. If UPC resolves to < 3.5 and creatinine to ≤ 1.5 × institutional ULN, resume cediranib with reduction in cediranib by one dose level. Consider consultation with nephrologist.
: If UPC is < 1 and creatinine > 1.5 × institutional ULN, AE management should be followed as per* **Table 6.	

Table 11: Management of Thyroid Toxicities (Associated with Cediranib)	
Result of TSH, T4, and T3	**Management Guidelines**
Referral to an endocrinologist should be considered if thyroid abnormalities occur. Patients already on thyroid replacement hormone who require adjustment of their replacement regimen will be considered to have a drug-related toxicity.	
Increase in TSH with normal T4/T3	Maintain study drug dosing unless hold is otherwise clinically indicated. Continue to monitor.
Increase in TSH with normal T4/T3 and adverse events suggestive of incipient	Consider replacement thyroxine.

Table 11: Management of Thyroid Toxicities (Associated with Cediranib)	
Result of TSH, T4, and T3	**Management Guidelines**
hypothyroidism	Maintain study drug dosing unless hold is otherwise clinically indicated.
Increase in TSH with reductions in T4 and T3	Consider replacement thyroxine. Maintain study drug dosing unless hold is otherwise clinically indicated.

Table 12: Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Posterior reversible encephalopathy syndrome (PRES) has been uncommonly reported in clinical studies with cediranib. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances, and can be fatal. Mild to severe hypertension may be present. In patients developing PRES, treatment of specific symptoms including control of BP is recommended. Confirmation of PRES requires brain imaging, preferably MRI. Cediranib should be discontinued following confirmation of PRES. The safety of reinitiating cediranib in patients previously experiencing PRES is not known. After consultation with the Overall PI and the NCI, consideration of restarting the study drugs may be evaluated in light of any clinical benefit.

Table 13: Gastrointestinal Perforation
Gastrointestinal perforation, sometimes associated with fistula formation, has been observed in patients receiving cediranib. Some events of gastrointestinal perforation have been fatal but causality could not be unequivocally assigned to cediranib. Cediranib should be used with caution in patients at risk and should be permanently discontinued in those patients who experienced gastrointestinal perforation or fistula. All events of gastrointestinal perforation are followed-up and an assessment should be made on their relationship to the underlying tumor.

Table 14: Decreased LVEF			
Relationship to Institution's LLN	**LVEF Decrease < 10% from screening value**	**LVEF Decrease 10 – 15% from screening value**	**LVEF Decrease ≥ 16% from screening value**
Patients who have any of the following should undergo an echocardiogram (ECHO) or MUGA at baseline and every four cycles while on study: • Prior treatment with anthracyclines • Prior treatment with trastuzumab • Prior central thoracic radiation therapy (RT), including RT to the heart			

Table 14: Decreased LVEF			
Relationship to Institution's LLN	**LVEF Decrease < 10% from screening value**	**LVEF Decrease 10 – 15% from screening value**	**LVEF Decrease ≥ 16% from screening value**
• History of myocardial infarction within 12 months prior to study entry 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 this table. If the institution's LLN is not specified, an LVEF of 50% should be considered the LLN threshold.			
Normal	Maintain study drug dosing unless hold is otherwise clinically indicated.	Maintain study drug dosing unless hold is otherwise clinically indicated.	Maintain study drug dosing unless hold is otherwise clinically indicated. Repeat MUGA/ECHO within 3 cycles.
1-5% below LLN	Maintain study drug dosing unless hold is otherwise clinically indicated. Repeat MUGA/ECHO within 3 weeks.	Maintain study drug dosing unless hold is otherwise clinically indicated. Repeat MUGA/ECHO within 3 weeks.	Hold study medications and repeat MUGA/ECHO within 3 weeks.
≥ 6% below LLN	Maintain study drug dosing unless hold is otherwise clinically indicated. Repeat MUGA/ECHO within 3 weeks.	Hold study medications and repeat MUGA/ECHO within 3 weeks.	Hold study medications and repeat MUGA/ECHO within 3 weeks.

Table 15: Rotator Cuff Injury (Associated with Cediranib and Olaparib)	
Event Description	**Management Guidelines**
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.	
Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Maintain study drug dosing unless hold is otherwise clinically indicated.

Table 15: Rotator Cuff Injury (Associated with Cediranib and Olaparib)	
Event Description	**Management Guidelines**
	Limit heavy lifting or carrying of heavy objects, bags, or backpacks. Consider shoulder MRI if symptoms warrant.
Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Hold cediranib and olaparib for up to 14 days until symptoms resolve to ≤ Grade 1 or baseline. Cediranib and olaparib may then be resumed at a reduced dose level of both study drugs. Obtain shoulder MRI if not previously obtained. If rotator cuff injury present on MRI, refer for physical therapy as clinically indicated.
Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL.	Hold cediranib and olaparib for up to 14 days until symptoms resolve to ≤ Grade 1 or baseline. Cediranib and olaparib may then be resumed at a reduced dose level of both study drugs after discussion with the overall PI.

Table 16: Myelodysplastic Syndrome (Associated with Olaparib)
Myelodysplastic syndrome (MDS) has been described in patients receiving olaparib. To monitor for any potential development of MDS, patients who have treatment held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery. If counts do not improve to CTCAE grade 1 or better despite drug cessation for 4 weeks, patients should be referred to a hematologist for further assessment. A bone marrow analysis should be considered per hematology assessment. Patients who develop MDS/AML on treatment should be discontinued from olaparib treatment and managed appropriately.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs,

the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

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

7.1.1.1 CAEPR for Cediranib

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			

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

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

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

[3]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation,

Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (polycythemia); Bone marrow hypocellular; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (premature ventricular complexes); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Mobitz (type) II atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ears feel full/plugged); Ear and labyrinth disorders - Other (viral labyrinthitis); Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (blindness); Eye disorders - Other (visual disturbance); Papilledema; Photophobia; Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Bloating; Colitis; Colonic obstruction; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Flatulence; Gastric necrosis; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (hydrops); Gastrointestinal disorders - Other (tongue sensitivity); Ileus; Oral pain; Periodontal disease; Peritoneal necrosis; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Fever; Gait disturbance; Hypothermia; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder obstruction; Hepatic pain; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice cholestatic)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture; Injury, poisoning and procedural complications - Other (tracheostomy malfunction); Intestinal stoma leak; Venous injury; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Hemoglobin increased; INR increased; Investigations - Other (elevated ammonia level); Investigations - Other (increased blood erythropoietin); Lipase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Avascular necrosis; Back

pain; Bone pain; Chest wall pain; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Myalgia; Myositis; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Central nervous system necrosis; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Encephalopathy; Hydrocephalus; Ischemia cerebrovascular; Memory impairment; Muscle weakness left-sided; Nervous system disorders - Other (coma); Nervous system disorders - Other (right hemiparesis); Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Spinal cord compression; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Confusion; Delirium; Depression; Hallucinations; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Cystitis noninfective; Hematuria; Urinary retention; Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Menorrhagia; Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fistula; Pulmonary hypertension; Sinus pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pruritus; Purpura; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (petechiae); Skin and subcutaneous tissue disorders - Other (plantar warts); Skin ulceration; Urticaria
VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hypotension; Vasculitis

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

7.1.1.2 CAEPR for Olaparib

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2073 patients*. Below is the CAEPR for Olaparib (AZD2281).

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

Version 2.4, April 24, 2019 [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 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea			***Nausea (Gr3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
	Creatinine increased		
	Lymphocyte count decreased		
	Neutrophil count decreased		
	Platelet count decreased		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	

NOTE: New Primary Malignancies other than MDS/AML
New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary

malignancy in all cases, including documented *BRCA* mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib.

[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; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Bone pain; Generalized muscle weakness; Muscle cramp; 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; Pruritis; Rash maculo-papular
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: Olaparib (AZD2281) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in

events never previously associated with either agent.

7.1.1.3 Adverse Event List(s) for Cisplatin, Carboplatin, and Etoposide

For risks associated with cisplatin, carboplatin, or etoposide, please refer to the respective package inserts.

7.2 Adverse Event Characteristics

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

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

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

7.3 Expedited Adverse Event Reporting

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

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

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

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

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

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes

Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
5.0	Grade 3-4 hematologic toxicities not requiring hospitalization that last < 7 days	3-4	n/a	chemotherapy	
5.0	Alopecia	any			

7.4 Routine Adverse Event Reporting

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

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

7.5 Reporting of Pregnancy and Overdose

In the event of subject overdose with olaparib and/or cediranib, the trial Principal Investigator, Dr. Jacob Sands, must be notified within 24 hours regardless if the event presents an adverse event of any grade. The trial Principal Investigator will be responsible for collecting and reporting all event data to the NCI.

In the event of subject pregnancy while on trial, the trial Principal Investigator, Dr. Jacob Sands, must be notified within 24 hours of learning of the event, whether or not it meets criteria for the reporting of an adverse event. The site should follow the pregnancy until the completion or the pregnancy is terminated. The trial Principal Investigator will be responsible for collecting and reporting all event data to the NCI.

7.6 Secondary Malignancy

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

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

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

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

7.7 Second Malignancy

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

reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agents

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

8.1.1 Cediranib (AZD2171, NSC # 732208)

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

Other Names: Cediranib, AZD2171 maleate

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

Molecular Formula: C25H27FN4O3 • C4H4O4

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

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

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

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

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

iron oxide, and titanium dioxide.

Storage: Store intact bottles at controlled room temperature 20°C to 25°C (68 to 77°F) and protect from light and moisture.

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

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

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

Potential Drug Interactions: AZD2171 (cediranib) is primarily metabolized by flavin-containing monooxygenase enzymes (FMO1 and FMO3) and UGT1A4. It is not a substrate of CYP450 enzymes. In vitro studies suggest that AZD2171 (cediranib) is a substrate for P-glycoprotein (Pgp), but not breast cancer resistance protein (BCRP). Since clinically relevant induction or inhibition of FMO enzymes is uncommon, use caution in patients taking concomitant medications that are strong inhibitors (e.g. ketoconazole) or strong inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's Wort) of UGT1A4 or Pgp in particular. If chronic concomitant administration of strong inducers or inhibitors is unavoidable, consult the protocol document and/or the principal investigator before making any dose adjustments.

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

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

AZD2171 (cediranib) is approximately 95% bound to human plasma proteins, with human serum albumin and α1-acid glycoprotein accounting for most of this binding. Use caution in patients taking concomitant medications with narrow therapeutic ranges that are also highly protein-bound.

Anticoagulants are not absolutely contraindicated during treatment with AZD2171 (cediranib); however, use AZD2171 (cediranib) with caution and increase monitoring in patients while on study. Please see Section 5.2. Patients who receive VEGF inhibitors are at increased risk of bleeding and hemorrhage.

Patient Care Implications: Agents that inhibit VEGF signaling have the potential to affect wound healing. For patients already enrolled onto the protocol, the manufacturer recommends holding AZD2171 (cediranib) for 2 weeks prior to elective surgery and restarting when the surgical wound is healed. Protocol exclusion criteria include patients who have had major thoracic or abdominal surgery within 4 weeks prior to start of study or patients with any surgical incision that is not fully healed.

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

Availability: Cediranib is provided to the NCI under a Collaborative Agreement between AstraZeneca (the Pharmaceutical Collaborator) and the DCTD, NCI (see Section 12.4).

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

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

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

Investigator Brochure Availability: The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the

establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts:

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- PMB IB Coordinator: IBcoordinator@mail.nih.gov

8.1.2 Olaparib (AZD2281, NSC 747856)

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

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

Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

Molecular Formula: C24H23FN4O3

Molecular Weight: 434.46

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

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

Description: Crystalline solid

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

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

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

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

Storage: Store in a secure location below 30° C (86° F). Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.

Stability: Shelf-life studies are ongoing. If a storage temperature excursion is identified, promptly return olaparib to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Route of Administration: Tablets can be taken by mouth with a light meal/snack.

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

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

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

Olaparib is also an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, multi-drug and toxin

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

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

Because the adverse events related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery.

Availability: Olaparib is provided to the NCI under a Collaborative Agreement between AstraZeneca (the Pharmaceutical Collaborator) and the DCTD, NCI (see Section 12.4).

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

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Records for each agent, strength, formulation and ordering investigator on this protocol.

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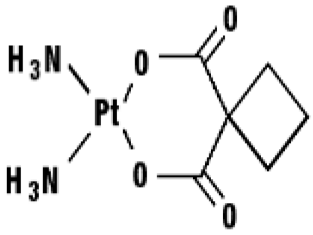
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov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

8.2 Commercial Agents

8.2.1 Carboplatin

Product description: A commercially available agent supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin. Carboplatin is a platinum coordination compound. The chemical name for carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0í]-,(SP-4-2), and carboplatin has the following structural formula:



Carboplatin is a crystalline powder with the molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and

dimethylacetamide. Please see FDA package insert.

Solution preparation: Please see FDA package insert. Supplied as a premixed aqueous solution of 10 mg/mL carboplatin.

Carboplatin can be further diluted to concentrations as low as 0.5 mg/mL with 5% dextrose in water (D5W) or 0.9% sodium chloride injection, USP.

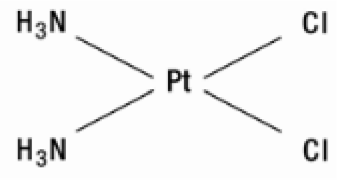
Route of administration: Intravenous, administer as per institutional standards.

Agent Ordering: Commercially available agent

8.2.2 Cisplatin

Product Description: A commercially available clear, colorless, sterile aqueous solution available in amber vials. Each 50 mL amber vial of infusion concentrate contains: 1 mg/mL cisplatin, 9 mg/mL Sodium Chloride, hydrochloric acid and sodium hydroxide to approximate pH of 4.0, and water for injection to a final volume of 50 mL.

The active ingredient, cisplatin, is a yellow to orange crystalline powder with the molecular formula PtCl2H6N2, and a molecular weight of 300.1. Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/mL and in dimethylformamide at 24 mg/mL. It has a melting point of 207°C. See FDA package insert.



Solution Preparation: Please see FDA package insert. 50 mg vials should be reconstituted with 50 mL of sterile water for injection. Caution should be exercised in handling the powder and preparing the solution of cisplatin. Procedures for proper handling and disposal of anticancer drugs should be utilized. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and IV sets containing cisplatin for injection.

Route of Administration: Intravenous, administer as per institutional standards in 0.9% NaCl, over 60 minutes.

Agent Ordering: Commercially available agent

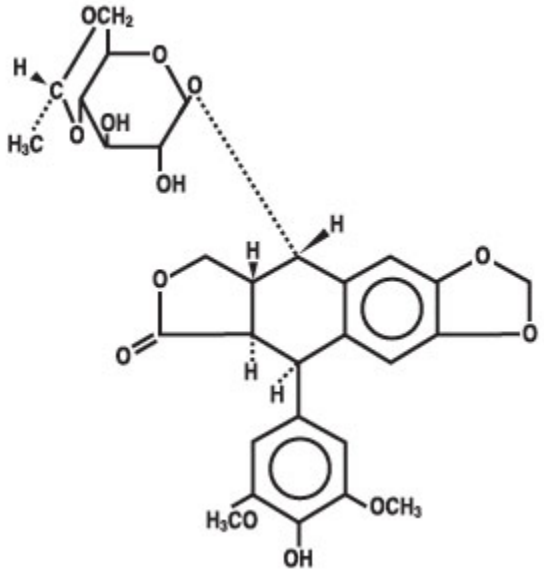
8.2.3 Etoposide

Product description: Etoposide for Injection (VP-16) is a commercially available antineoplastic agent which is available for intravenous infusion as a 20 mg/ml solution in 100 mg (5 ml), 500 mg (25 ml), or 1 gram (50 ml) sterile, multiple dose vials.

Etoposide (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is very soluble in methanol and chloroform, slightly soluble in ethanol, and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents.Please see FDA package insert.

The chemical name for etoposide is: It is 4'-demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-β-D-glucopyranoside].

Etoposide has the following structure:



Solution Preparation: Please see FDA package insert. Etoposide Injection, USP must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur.

Solutions of etoposide should be prepared in an aseptic manner. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Route of Administration: Intravenous, administer as per institutional standards in 0.9% NaCl over 60 minutes. Shorter administration times are not recommended as hypotension can occur with infusion times shorter than 30 minutes.

Solutions of etoposide should be prepared in an aseptic manner. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Route of Administration: Intravenous, administer as per institutional standards in 0.9% NaCl over 60 minutes. Shorter administration times are not recommended as hypotension can occur with infusion times shorter than 30 minutes.

Agent Ordering: Commercially available agent

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Please see Section **2.4** for detailed background information for all correlative studies.

9.1 Archival Tumor Tissue Collection - Exploratory/Ancillary Correlative Studies

Archival tumor tissue collection is required for all participants enrolling to the trial, ideally 20 5 micron slides. Confirmation that archival tissue is available is required for trial eligibility. Participants who do not have archival tissue available may undergo a fresh tumor biopsy if clinically feasible.

In the event that a participant has archival tissue available but does not have the minimum requested amount for every correlative study, priority should be as follows:

1. Whole exome sequencing and RNA seq (10 5 micron slides minimum, 15 preferred)
2. PARP/SLFN11 immunohistochemistry (4-5 5 micron slides)
3. BROCA-HR (2 consecutive unstained 10 micron slides or 4 consecutive 5 micron slides)

If there is remaining tumor tissue that can be sent to the ECTCN biorepository for storage and DNA/RNA extraction, this should be done. Otherwise, any remaining DNA/RNA after planned analyses at the Broad or University of Washington will be sent to this ECTCN biorepository.

9.2 Specimen requirements

Overview of sample requirements

Study	Required Specimen	Collection Time Points	Collection Details
BROCA-HR	7 mL whole blood	Baseline	Collect in yellow top (ACD solution A) tube. Specimen to be shipped at ambient temperature for overnight

	FFPE slides (from primary tumor and/or metastatic sites)	Archival	4-5 consecutive unstained 10 µm slides should be provided and shipped at ambient temperature overnight
Plasma Angiome	Two 4mL tubes of blood	Baseline, Cycle 2 Day 1 of treatment, at time of progression	Collect in purple top tubes. Specimens should be processed on site to obtain plasma and then shipped on dry ice overnight.
Whole exome sequencing (WES) and RNAseq	FFPE slides	Archival	10 unstained slides of 5-10 micron thickness should be provided and shipped at ambient temperature overnight
Whole exome sequencing (WES) and RNAseq	Biopsy specimen (if obtained)	Pre-treatment; Post-progression (optional)	2 fresh frozen cores. Samples should be shipped by courier on dry ice for overnight delivery.
Sequencing (ultra-low pass +/-WES)	10 ml whole blood	Baseline, Cycle 2 Day1, cycle 3 Day1, then cycle 2 and 3 day 1 during maintenance and at end of study	Blood will be collected in 10 cc EDTA tubes, processed on site (spun with plasma then aliquotted) and then shipped on dry ice.

9.2.1 Tumor PARP Immunohistochemistry – Exploratory/Ancillary Laboratory Correlative Study #1

Collection of Specimen: A minimum of 3 5 micron unstained slides should be obtained for analysis.

Handling of Specimens: Specimens should be labeled with the NCI protocol number, study subject number, and "PARP IHC."

Samples will be subjected to immunohistochemistry (IHC) using total PARP1 antibody (Thermo Fisher, Freemont, CA) (used in prior studies, fresh Ab will be ordered when ready to perform IHC on study samples) (Byers, Cancer Discovery 2012). Antigen retrieval will be performed using a decloaker with Dako Target Retrieval pH 6.0.

SLFN11 IHC will be performed on FFPE specimens using fresh antibody as above against SLFN11 (HPA0203030, Sigma Aldrich)

Shipping of Specimens: Specimens should be shipped at room temperature. Samples may be shipped to:

Center for Biospecimen Research & Development (CBRD)
Attn: Kelsey Weren
NYU Langone Medical Center: Medical Science Building
550 First Avenue, Berg 3rd Fl., Rm. 381
New York, NY 10016
Lab: 212-263-0135
CBRD Main line: 646-501-4268
CBRD Fax: 646-501-4579

Sites Performing Correlative Study: PARP IHC will be performed in the laboratory of Dr. Lauren Byers at MD Anderson Cancer Center.

9.2.2 Whole Exome Sequencing and Whole Transcriptome Sequencing from Tissue – Exploratory/Ancillary Laboratory Correlative Study #2

Collection of Specimens: A minimum of 10 unstained slides of 5 micron thickness should be obtained for analysis. 15 slides strongly preferred.

Concomitant blood for germline DNA will be collected in 10 cc EDTA tube. 1mL of whole blood from this same tube will be banked from each tube at BASELINE ONLY.

Handling of Specimens: The Broad Institute has designed a portal through which information on patient samples can be directly entered and downstream results can be obtained. The following information is received securely through the portal:

Test Requisition Submission: All test requests for the Clinical Sequencing are received through the CRSP Client Portal. An authorized individual representing either a requisitioning physician or referring CLIA-certified laboratory may submit test requisitions via the CRSP Portal. Once the pertinent information for the requisitioning individual (i.e., NPI & medical license numbers) or entity (CLIA certificate number) has been verified, the client will be supplied with the information (username/password) required to access the CRSP Client Portal. Submission of a test requisition through the CRSP Client Portal ensures that all required requisition elements (e.g. Patient and sample information and identifiers) are completed and are in an acceptable format.

Patient Information: Patient information will be de-identified to the sequencing center. We will store only the information provided and utilize IDs assigned by the clinical centers. We note that for our standard test requisitions we have made available a portal through which physicians can supply patient identifying information that will be stored securely in a compliant manner. This information is supplied in the form of a unique alphanumeric identifier (supplied by the requisitioning individual/entity) or the more standard collection of personal identifiers (e.g. first name, last name, date of birth, address, telephone number). The requisitioning individual/entity also completes an

attestation that the patient or legal representative has been informed of the potential risks and benefits of undergoing genetic testing and has consented to such testing

Sample Information: The type of sample (DNA, EDTA-anticoagulated whole blood or Saliva) being submitted for testing will be supplied. If a unique alphanumeric patient identifier is being used, a distinct sample identifier will also be supplied. Finally, the sample collection date will also be noted on the test requisition form.
Sample management and QC: Sample handling will be performed by the CLIA-certified lab within the Broad Institute's Genomics Platform and includes an industry-grade high throughput registration, processing, and tracking system for biological samples. The system includes multiple points of quality control (i.e., sample quantitation, tracking, and genetic fingerprinting), allowing receipt and processing of an average of 16,000 samples per month. On arrival, each sample is assigned a unique bar code and entered into a validated database for sample analysis coupled to a bar code tracking system that records sample information (e.g., source, histology, clinical data), nucleic acid quality control information (e.g., genotyping, PCR), location information (e.g., freezer, shelf, rack), and project information. The database is linked directly to the LIMS systems for array and sequencing analysis.

For each DNA sample (optimized fingerprinting and WES processes require 50 to 100ng input DNA) received, the following steps will be performed:

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

Targeting the exome by hybrid selection: Whole exome targeting reagents from Illumina will be used to prepare the sample libraries. The Illumina targeting process employs capture principles similar to those we developed and licensed to Agilent Technologies for the SureSelect® hybrid selection method but uses DNA instead of RNA oligonucleotides or baits for target capture. The 'Rapid Capture Exome' content was co-developed by the Broad Institute with Illumina. The Broad Institute's proprietary process enhancements to the 'Rapid Capture Exome' protocol makes use of these capture reagents along with their OneWell 'with-bead' library construction protocol and a specialized dual-indexing step for an extra level of contamination control. Briefly, the fully automated LIMS-tracked process begins with 100ng of Picogreen-quantified genomic DNA (in special cases as little as 50 ng of DNA). The genomic DNA is fragmented, using Covaris acoustic shearing, to the desired size of 150bp. Fragments are selectively bound to SPRI magnetic beads, followed by clean-up or washing steps, end repair, A-base addition, and indexed dual-adapter ligation. Following these steps the prepared DNA fragments are eluted from the SPRI beads and PCR amplified, generating 'pond' libraries ready for downstream hybrid capture. Pools of 12 indexed pond libraries then undergo two rounds of

hybridization and 'capture' in which the pond pools are hybridized to the biotinylated exome baits, captured on streptavidin beads, washed at high stringency to remove off-target hybridizations, and then eluted from the SPRI beads. This process hybridization, washing, and elution is repeated once more and, following the second elution step, captured targets are PCR amplified, cleaned up one final time, and then submitted for sequencing.

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

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

On-target sequence yield. A major inefficiency of all massively parallel targeting approaches is the inability to precisely and uniquely capture (to the base pair) the target of interest. We have made a number of improvements to our production protocol (such as blocking agents against sequencing adaptors) which have resulted in routine on-target proportion of ~ 90% of reads.

Percent-target coverage ≥20X. We require the baseline coverage to be >80% of targets to be covered at over 20X across the target region. This level of coverage typically results in ~100X average coverage across the exome, though higher levels of coverage can be achieved with additional sequencing.

Non-duplicate reads. Observation of duplicate reads (reads with the same start and stop sites) indicates that the same molecule has been sequenced multiple times. This can mislead SNP calling algorithms, since the same molecule-specific (PCR or other) error can erroneously be counted as independent observations. We found that PCR upstream of selection can lead to a high degree of duplication, likely from bottlenecking of input material. Our current protocol is stable at 5-10% read duplication (duplicated reads are removed bioinformatically at BAM aggregation) and an increase in this measure signals issues with library preparation.

Contamination check. As an additional layer of process control and test accuracy, we routinely apply a set of algorithms called 'verifyBamID' to every sequencing dataset. VerifyBamID is a piece of software that detects possible sample mixture from population allele frequency only, which may be particularly useful when the genotype data is not available. Specifically VerifyBamID verifies whether the reads in a particular file match previously known genotypes for an individual (or group of individuals), and checks whether the reads are contaminated as a mixture of two samples8. Using a mathematical model that relates observed sequence reads to a hypothetical true genotype, verifyBamID determines whether sequence reads obtained from the processing of a given sample match a particular individual or are more likely to be contaminated, derived from a closely related individual, or derived from a completely different individual.

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

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

The CSRP's tools are of the highest quality in the field and were used to analyze a large number of cancer projects (references available upon request). For example, comparison of MuTect (CSRP's mutation caller) to other commonly used tools demonstrated that it is vastly superior (much more sensitive for any given false-positive value) (Figure 2). Finally, the Broad Institute is developing tools to take all types of alterations in a patient's tumor and prioritize the events with respect to clinical-relevance. These are then presented in a comprehensive report. Other tools that are being developed are aimed at analysis of sub-clonal composition of tumors and their evolution in multiple tumor samples (e.g. longitudinal samples, primary/metastases, primary/relapse etc.). These tools can estimate the number of macroscopic sub-clones and the fraction of cancer cells that they represent and when multiple tumors are analyzed the tools can also detect evolution of sub-clones (Landau, Carter, Stojanov et al.)

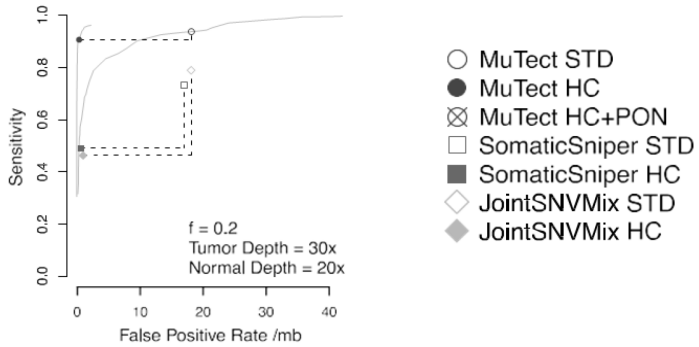


Figure 2: Receiver operating characteristic (ROC) curve for MuTect, for mutations at allele fraction of 0.2 and at 30x sequencing depth. Results are shown for Standard filtering (STD) and High-Confidence (HC). Results for two leading tools in the field, SomaticSniper and JointSVNMix are provided showing significant improved sensitivity for MuTect compared to the other tools.

Transcriptome sequencing (RNA-seq): We will also generate transcriptome sequencing using tumor RNA obtained from biopsies. RNA- seq may provide insights into overexpressed genes, chimeric transcripts (possibly indicative of underlying structural genomic rearrangements), and/or alternatively spliced variants. Thus, application of RNA-seq to serially obtained biopsies may provide useful information about dysregulated pathways or networks not evident from somatic genetic analysis, pharmacodynamic changes caused by drug action, adaptive cellular responses to drug target inhibition, and "non- genetic" resistance mechanisms. As with WES, the Broad Institute has developed considerable "production-scale" expertise in RNA-seq sequencing. As the production center for the Genotype Tissue Expression (GTEx) project (http://commonfund.nih.gov/GTEx/), the Broad Institute has developed many RNA-seq protocols. In addition to the GTEx project, the Broad also produced RNA-seq data for the entire Cancer Cell Line Encyclopedia (CCLE). Over the past two years, the Broad Institute generated RNA-seq data for over 3,000 samples. Through application of automated fluid- handling techniques and process optimization, they created an RNA-seq sample preparation pipeline that can handle 192 samples per week at current demand levels.

Illumina's TruSeq method affords robust performance in terms of RNA input and sequencing library complexity. This method allows for input RNA amounts as low as 250-500 ng and is automated for high-throughput production. To generate RNA-seq data, polyA+ RNA will be isolated in the Genetic Analysis Platform at the Broad Institute. Next, strand-specific cDNA libraries will be generated. Each cDNA library will be sheared by sonication, paired-end adapters for Illumina sequencing will be added, and Illumina sequencing libraries will be prepared following established protocols. Each sample will be subjected to Illumina sequencing using an Illumina HiSeq instrument, producing ~101 bp paired-end reads. RNA-seq data will be analyzed by the Computational Biology Core.

As with WES, the Broad Institute has developed considerable "production-scale" expertise in RNA sequencing. Illumina's TruSeq method affords robust performance in

terms of RNA input and sequencing library complexity. This method allows for input RNA amounts as low as 250- 500ng and is automated for high-throughput production. Algorithms to identify RNA-based features including alternative splice variants, novel fusions and aggregate gene expression changes (CuffLinks/CuffDiff) will be applied to RNA-seq data.

Shipping of Specimens: Please refer to the Specimen Requirements table in section 9.2 for specific shipping requirements. Samples should be shipped to:

Broad Institute
Attn: Genomics Platform—Samples Lab
320 Charles Street—Lab 181
Cambridge, MA 02141
Phone (617) 714-8952

Site(s) Performing Correlative Study: WES and RNASeq will be performed by the Center for Cancer Precision Medicine at the Broad Institute (Cambridge, MA).

9.2.3 BROCA-HR – Exploratory/Ancillary Laboratory Correlative Study #3

Collection of Specimen: A minimum of 2 consecutive unstained 10 µm slides should be obtained for analysis.

Handling of Specimens: Specimens should be labeled with the NCI protocol number, study subject number, and "BROCA-HR."

DNA will be extracted from PBMCs and FFPE archived tumor tissue containing at least 30% tumor nuclei. A targeted capture and massively parallel sequencing approach called BROCA1 will be applied to samples. For the proposed study, a more recent version of BROCA with 55 genes (BROCA-HR) that serve as a single assay to test for inherited risk of ovarian carcinoma and for germline and somatic mutations that influence response to therapy will be utilized.
Library preparation has been fully automated to increase sample turnaround and lower cost. Paired-end libraries with 350bp inserts will be prepared from 1ug of constitutional or neoplastic DNA and hybridize to a custom pool of oligonucleotides targeting genomic regions as previously described (27) using the SureSelectXT enrichment system on a Bravo liquid-handling instrument (Agilent). Following capture, samples will be barcoded with 48 different indexed primers. The pooled samples are sequenced on a single lane of a HiSeq flowcell (Illumina) with 2x101bp paired end reads and a 7bp index read to allow for de-multiplexing and binning of individual samples. Single nucleotide variants and insertions and deletions will be detected as previously described with some updates in the bioinformatics pipeline (27). Deletions and duplications of exons will be detected by a combination of depth of coverage and split read analysis as previously described (39), supplemented with additional alignments generated by SLOPE (40).
All germline loss of function mutations in cancer susceptibility genes will be confirmed with PCR amplification and Sanger sequencing. Cases will be identified as HR proficient or deficient based on sequencing data of known Fanconi anemia (FA)-BRCA genes and

then correlate HR proficiency with response to platinum or PARPi on the trial. Later, in exploratory analyses, we will add in analyses of NHEJ and other modifying genes, genomic scarring, or other somatic tests by our lab or others to complement the determination of HR deficiency.

Shipping of Specimens: Please refer to the Specimen Requirements table in Section 9.2 for specific shipping requirements.

Sites Performing Correlative Study: BROCA-HR will be performed by the laboratory of Dr. Elizabeth Swisher at the University of Washington (Seattle, WA). Samples should be shipped to:

Swisher Lab
ATTN: Kathy Agnew
University of Washington
1959 NE Pacific Street
HSB BB632
Seattle, WA 98195
Phone (206) 685-7927
Kagnew@uw.edu

9.3 Blood-Based Exploratory/Ancillary Correlative Studies

9.3.1 Plasma Angiome Analysis – Exploratory/Ancillary Laboratory Correlative Study #4

Collection of Specimens: Blood samples to be collected at the following time points:

Table 17: Plasma Angiome Collection Schedule

Trial Phase	Visit Day	Time Point	Sample Number
Initial therapy	Cycle 1 Day 1	Any time prior to dosing with any of the agents	1
Initial therapy	Cycle 2 Day 1	Any time prior to dosing with any of the agents	2
Maintenance	Cycle 2 Day 1*	Any time prior to dosing with any of the agents	3
Initial therapy ***OR*** maintenance	Time of Disease Progression	Any time during the visit	4
**: In participants not receiving maintenance therapy, "Cycle 2 Day 1" sample to be collected 6 weeks after the completion of the initial therapy phase of the trial.*			

Blood for each time point should be collected in two 4 mL purple top tubes as described below.

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

1. Draw two 4ml purple top (K2EDTA) tubes (BD Vacutainer, Catalog no. 367861)
2. Invert tubes 10 times to mix blood
3. Centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
4. Remove plasma from each tube and transfer equally into two separate clean 15ml polypropylene tubes
5. Repeat centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
6. Aliquot approximately 1.0ml of plasma from each tube into each 2.0ml cryovial. For the EDTA, aliquot into pink capped cryovial. Total of 4 pink capped cryovials needed for EDTA plasma.
7. Label and freeze at - 80°C* (see labeling instructions below)

*Please note: If your site does not have a -80°C freezer, samples should be shipped on dry ice on the day of collection. If unable to ship samples on the day of collection, please place the samples on dry ice until they can be shipped. Samples can be stored on dry ice for no more than 48 hours prior to shipping. Please replenish dry ice as needed to ensure samples stay frozen and there is enough to last throughout shipment.

Plasma-containing tubes should be labeled with the following information (using a Sharpie or Cryopen):

- Protocol Name
- Subject Study Number
- Subject initials
- Sample date and time
- Sample type (e.g. EDTA plasma, whole blood, citrate plasma, etc.)

Shipping of Specimens: Samples should be shipped within 48 to 72 hours of completed processing. All biomarker samples must be shipped on dry ice by overnight delivery Monday through Thursday (no holidays) to the following address:

Attention: **Phase I Biomarker Laboratory**
ATTN: Andrew Nixon, PhD
Duke University Medical Center
395 MSRB 1,
203 Research Drive
Durham, NC 27710
Phone (919) 681-2239
Email contact: Chris Brady: jchris.brady@duke.edu

Sites Performing Correlative Study: This correlative analysis will be performed in the laboratory of Dr. Andrew Nixon at Duke University Medical Center.

9.3.2 Circulating Free DNA (cfDNA) – Exploratory/Ancillary Laboratory Correlative Study #5

Collection and Handling of Specimens: Blood samples to be collected at the following time points:

Table 18: cfDNA Collection Schedule

Trial Phase	Visit Day	Time Point	Sample Number
Initial therapy	Cycle 1 Day 1	Any time prior to dosing with any of the agents	1
Initial therapy	Cycle 2 Day 1	Any time prior to dosing with any of the agents	2
Initial Therapy	Cycle 3 Day 1	Any time prior to dosing with any of the agents	3
Maintenance	Cycle 2 Day 1*	Any time prior to dosing with any of the agents	4
Maintenance	Cycle 3 Day 1	Any time prior to dosing with any of the agents	5
Initial therapy ***OR*** maintenance	Time of Disease Progression	Any time during the visit	6

**: In participants not receiving maintenance therapy, a "Cycle 2 Day 1" sample is to be collected within 6 weeks of the completion of the initial therapy phase of the trial.*

NOTE: Time period from draw to freezing of plasma must be less than 3 hours. Blood will be collected in 10 cc EDTA tubes, barcoded, and processed within 3 hours of blood draw. We have previously confirmed that white blood cells remain stable during this period of time and thus, do not affect the purity of tumor-derived cell-free DNA. 1mL of whole blood will be banked from each tube and frozen at -80C in a 2d-barcoded tube until further processing. The remaining blood will be subjected to two rounds of centrifugation (2,000 x g for 10 min followed by 15,000 x g for 10min). Plasma will be removed and frozen at -80C in another 2d-barcoded tube until further processing. All samples are registered in our laboratory information management system and tracked throughout the process. Extractions of cell-free DNA and germline DNA will be performed from banked plasma and whole blood, respectively, using an automated liquid handler. Liquid handling systems will also be used for the subsequent steps of quantification, normalization, and library construction. Sequencing on the Illumina HiSeq will be used to assess the purity of tumor-derived cell-free DNA. Samples with sufficient

purity of tumor-derived cell-free DNA will be nominated for hybrid capture of the entire human exome and sequenced on the Illumina HiSeq.

Shipping of Specimens: Specimens should be shipped at -70°C or colder

Sites Performing Correlative Study: Circulating free DNA processing and assessment of tumor DNA purity as well as subsequent whole exome sequencing will be performed by the Center for Cancer Precision Medicine at the Broad Institute (Cambridge, MA).

Shipping of Specimens: Please refer to the Specimen Requirements table in section 9.2 for specific shipping requirements. Samples should be shipped to:

Broad Institute
Attn: Genomics Platform—Samples Lab
320 Charles Street—Lab 181
Cambridge, MA 02141

9.3.3 Circulating Tumor Cells for Cell Derived Xenograft Models – Exploratory/Ancillary Laboratory Correlative Study #5

Collection of circulating tumor cells (CTCs) will be optional for all participants enrolled to the trial as part of a companion study NCI 9846. Patients will be asked to sign the protocol informed consent form to allow collection and use of samples to generate patient-derived models (cell lines) and the collection of associated limited medical information. Patients will not be able revoke their consent for research use of these samples once collected; this is specified in the informed consent form.

Samples will be collected on the SAME schedule as described in table 19 (section 9.3.2)

9.4 Fresh Tumor Tissue Collection - Exploratory/Ancillary Correlative Studies

9.4.1 Tumor PARP Immunohistochemistry, BROCA-HR, and WES

Participants able and willing to undergo optional fresh tumor biopsies may have the fresh samples sent for Tumor PARP immunohistochemistry, BROCA-HR, and WES analysis as previously described.

Collection of Specimens: Optional fresh biopsies will be obtained prior to entry on study, anytime between cycle 1 day 8 and cycle 2 day 1, and at the time of disease progression when clinically feasible. Time of progression biopsy should be obtained prior to the initiation of another anti-cancer therapy. In the event that it is not clinically possible to obtain a biopsy before the initiation of another treatment, the time of progression biopsy may be obtained any time up to 14 days after the last dose of study medication.

Collection of fresh tumor tissue by core biopsy, surgical resection, fine needle aspiration (FNA), or drainage of effusions should be performed according to local standards at each participating site. Whenever possible, core biopsy samples should be collected for analysis. Four biopsy passes utilizing a 16-18 gauge needle are preferable, but 20 gauge core needle biopsies are also acceptable at the discretion of the interventionalist performing the biopsy procedure.

If a core biopsy is judged to be too unsafe or difficult for the participant in the opinion of the treating investigator or interventionalist performing the procedure, an FNA or cytology sample can also be collected. The goal for a thoracentesis or paracentesis procedure will be 500 – 1000 mL collected in a standard collection tube. The goal for an FNA will be three distinct passes. Less than the goal amount of tissue is acceptable for any of the biopsy collection methods, and should be based upon the clinical judgment of the treating investigator and the clinician performing the procedure.

Handling of Specimens: Cytology samples should be made into blocks per routine local procedures.

Research cores should be allocated in the following order:

1. Core #1 and 2: Placed in neutral buffered formalin and then embedded in FFPE (Formalin Fixed Paraffin Embedded) no more than 16 hours after exposure to neutral buffered formalin.
2. Cores #3 and 4: embedded in frozen OCT medium, transported and frozen on dry ice, stored at -80°C.

Shipping of Specimens: Please see section 9.2 for details on shipping requirements.
Samples should be shipped to:
Center for Biospecimen Research & Development (CBRD)
Attn: Kelsey Weren
NYU Langone Medical Center: Medical Science Building
550 First Avenue, Berg 3rd Fl., Rm. 381
New York, NY 10016
Lab: 212-263-0135
CBRD Main line: 646-501-4268
CBRD Fax: 646-501-4579

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Informed consent, scans, and x-rays must be done $\leq$4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Table 19: Study Calendar – Initial Therapy Phase									
	Pre-Study	**Cycle 1 Day 1**	**Cycle 1 Day 8[t]**	**Cycle 1 Day 15[t]**	**Cycle 2 Day 1[u]**	**Cycle 3 Day 1[u]**	**Cycle 4 Day 1[u]**	**Within 2 Weeks of Completion of Initial Therapy**	**Off Treatment[v]**
Cediranib[A]		*As described in Section5.1.1*							
Cisplatin/Carboplatin[B]		*As described in Section 5.1.3*							
Etoposide[B]		*As described in Section 5.1.5*							
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X----------							X
Physical exam	X	X			X				X
Vital signs[a]	X[b]	X[c]	X	X	X	X	X		X
Height	X								
Weight	X	X		X		X			X
Performance status (ECOG)	X	X			X	X	X		X
CBC w/diff, plts[d]	X	X	X	X	X	X	X		X
Serum chemistry[e]	X	X	X	X	X	X	X		X
Urinalysis[f]	X				X	X	X		X
TSH and Free T4[g]	X				X	X	X		X
Coagulation Panel[h]	X								
EKG[i]	X								
Adverse event evaluation	X	X----------							X
Initial Treatment Randomization[j]	X								
Tumor measurements	X	Tumor measurements are repeated every 6 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease. There is a ± 3 day scheduling window for obtaining tumor measurements.							X
Radiologic evaluation	X	CT or MRI imaging of every disease-involved site. Radiologic measurements should be performed every 6 weeks. There is a ±3 day scheduling window for obtaining scans.							X
β-HCG[k]	X								
Echocardiogram or MUGA[l]	X						X		
Home Blood Pressure Monitoring[m]		*As described in Section5.2.1.*							
Archival Tumor Tissue Collection[n]	X								
cfDNA Collection[o]		X			X	X			X
Plasma Angiome Analysis[p]		X			X				X
CTC Blood Collection[q]		X							X
Randomization to Maintenance Arm[r]								X	

Table 19: Study Calendar – Initial Therapy Phase

	Pre-Study	Cycle 1 Day 1	Cycle 1 Day 8[t]	Cycle 1 Day 15[t]	Cycle 2 Day 1[u]	Cycle 3 Day 1[u]	Cycle 4 Day 1[u]	Within 2 Weeks of Completion of Initial Therapy	Off Treatment[v]
Tumor Tissue Biopsy[s]	X				X				X

A: Cediranib: Dose as assigned; please see Section 2.2.1for treatment details.
B: Chemotherapy agents to be administered per standard of care guidelines, please see Section 5.1.3 for treatment details.
a. Vital signs to include heart rate, respiratory rate, blood pressure, temperature, and oxygen saturation (O_2 sat).
b. Screening blood pressure must be re-assessed on two occasions that are separated by a minimum of 1 hour.
c. For participants receiving cediranib: blood pressure on cycle 1 day 1 must be < 140/90 mmHg prior to dosing.
d. Additional time points as clinically indicated or as per standard of care.
e. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium. Additional tests and time points as clinically indicated or as per standard of care.
f. Urine protein:creatinine (UPC) ratio may be used instead. If urinalysis is performed for screening, test must be repeated with tests no less than 1 week apart. Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1 and off study urinalyses/UPC only required for patients receiving cediranib. Additional tests may be performed as clinically indicated.
g. Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, and off study TSH/Free T4 only required in patients receiving cediranib.
h. Coagulation panel to consist of aPTT, PT, and PT-INR.
i. Single EKG to be performed. EKG should be collected after the participant has been resting for at least 5 minutes.
j. Initial randomization to be performed after participant has satisfied eligibility requirements. Please see Section **4.3**for further detail.
k. Serum pregnancy test (women of childbearing potential).
l. Echocardiogram (echo) or MUGA required for all participants during screening. Repeat echo or MUGA required in participants with a prior history of treatment with anthracyclines, trastuzumab, central thoracic radiation therapy, or a history of myocardial infarction within 12 months prior to study entry.
m. Home blood pressure monitoring only required for participants randomized to receive cediranib.
n. Archival tumor tissue collection as described in Section 9.1
o. cfDNA to be collected any time prior to dosing with any of the agents on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1 as described in Section 1Additional sample to be collected at the time of disease progression.
p. Plasma angiome analysis to be collected any time prior to dosing with any of the agents on Cycle 1 Day 1 and Cycle 2 Day 1 as described in Section 9.3.1Additional sample to be collected at the time of disease progression.
q. CTC blood collection only required for participants who agreed to this optional additional research study. Samples to be collected any time prior to dosing with any of the agents on Cycle 1 Day 1 and again at the off study visit as described in Section 9
r. Participants who did not receive cediranib during the initial therapy phase who present with stable disease or better upon completion of initial therapy will be randomized to receive cediranib plus olaparib as maintenance therapy or no maintenance therapy, as discussed in Section 5.1Randomization to maintenance arm to occur within 2 weeks of completion of initial therapy.
s. Optional fresh tumor biopsy when clinically feasible as described in Section 9
t. A ± 2 day scheduling window exists for Cycle 1 Day 8 and Cycle 1 Day 15 to accommodate adverse weather, holidays, or other scheduling issues.
u. A ± 3 day scheduling window exists for the start of a subsequent cycle to accommodate adverse weather, holidays, or other scheduling issues.
v. Off treatment evaluation to be completed within 30 days of the last dose of study medication. Note: follow-up visits or other contact is required in order to identify SAEs during the 30 days following treatment.

Table 20: Study Calendar – Maintenance Phase

	Within 2 Weeks of Completion of Initial Therapy	Cycle 1 Day 1	Cycle 1 Day 8[m]	Cycle 1 Day 15[m]	Cycle 1 Day 22[m]	Cycle 2 Day 1[n]	Cycle 2 Day 15[m]	Cycle 3+ Day 1[n]	Off Treatment[o]	Every 3 months after discontinuing[p]
Cediranib[A§]		*As described in Section 5.1.1*								
Olaparib[A§]		*As described in Section 5.1.2*								
Randomization to Maintenance Therapy[a]	X									
Concomitant Medications	X----------X								X	
Adverse Event Assessment[§]	X----------X								X	
Vital Signs[b§]		X[c]	X	X	X	X	X	X	X	

Table 20: Study Calendar – Maintenance Phase

	Within 2 Weeks of Completion of Initial Therapy	Cycle 1 Day 1	Cycle 1 Day 8[m]	Cycle 1 Day 15[m]	Cycle 1 Day 22[m]	Cycle 2 Day 1[n]	Cycle 2 Day 15[m]	Cycle 3+ Day 1[n]	Off Treatment[o]	Every 3 months after discontinuing[p]
Physical Exam[§]		X		X		X		X	X	
Performance Status (ECOG)[§]		X				X		X		
Weight[§]		X	X	X	X	X	X	X	X	
CBC w/Diff, Platelets[§]		X	X	X	X	X	X	X	X	
Serum Chemistry[d§]		X	X	X	X	X	X	X	X	
TSH and Free T4[§]		X				X		X	X	
Urinalysis[e§]		X				X		X	X	
EKG[f§]		X						X[g]		
Echocardiogram or MUGA[§]								X[h]		
Home blood pressure monitoring[§]		*As described in Section 5.2.1*								
Tumor Measurements		Initial measurements for the maintenance phase to be conducted at the end of cycle 4 of the initial therapy phase. Subsequent tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease. There is a ± 7 day scheduling window for obtaining tumor measurements.							X	
Radiologic Evaluation		CT or MRI imaging of every disease-involved site. Participants should have imaging repeated prior to the initiation of maintenance therapy. Subsequent radiologic measurements during the maintenance phase should be performed every 8 weeks. After 6 months on maintenance therapy, scans may be performed every 12 weeks. There is a ±7 day scheduling window for obtaining scans.							X	
cfDNA Collection[i]						X		X[i]	X	
Plasma Angiome Analysis[j]						X			X	
CTC Blood Collection[k]									X	
Tumor Tissue Biopsy[l]									X	
Telephone or care provider contact										X

§: Denotes an assessment that is only required in participants who are receiving cediranib and olaparib.
A: Cediranib and Olaparib: Doses as assigned; please see Section 5.1.1 for treatment details.
a. Randomization to maintenance therapy to be completed within 2 weeks of completion of initial therapy, please see Section **5.1**for detail.
b. Vital signs to include heart rate, respiratory rate, blood pressure, temperature, and O_2 sat.
c. Blood pressure on cycle 1 day 1 must be < 140/90 mmHg prior to dosing with cediranib.
d. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Additional tests and time points as clinically indicated.
e. Urine protein:creatinine (UPC) ratio may be used instead.
f. Single EKG to be performed at each time point. EKG should be collected after the participant has been resting for at least 5 minutes.
g. EKG required on Cycle 3 Day 1 only. Additional EKGs to be collected as clinically indicated.
h. Echocardiogram or MUGA required once every four cycles (e.g., Cycle 4 Day 1, Cycle 8 Day 1, and so on) in participants with a prior history of treatment with anthracyclines, trastuzumab, central thoracic radiation therapy, or a history of myocardial infarction within 12 months prior to study entry.
i. cfDNA to be collected any time prior to dosing with any of the agents on Cycle 2 Day 1, on cycle 3 day 1, and at the off study visit as described in Section 9In participants not receiving maintenance therapy, a "Cycle 2 Day 1" sample should be collected within 6 weeks following the completion of the initial therapy phase of the study.
j. Plasma angiome analysis sample to be collected any time prior to dosing with any of the agents on Cycle 2 Day 1 and at the off study visit as described in Section 9.3. In participants not receiving maintenance therapy, the "Cycle 2 Day 1" sample should be collected 6 weeks following the completion of the initial therapy phase of the study.

Table 20: Study Calendar – Maintenance Phase

	Within 2 Weeks of Completion of Initial Therapy	Cycle 1 Day 1	Cycle 1 Day 8[m]	Cycle 1 Day 15[m]	Cycle 1 Day 22[m]	Cycle 2 Day 1[n]	Cycle 2 Day 15[m]	Cycle 3+ Day 1[n]	Off Treatment[o]	Every 3 months after discontinuing[p]

k. CTC blood collection only required for participants who agreed to this optional additional research study. Sample to be collected at the off study visit. Please see details in Section 9.3.1

l. Optional fresh tumor biopsy when clinically feasible as described in Section 9.4

m. A ± 3 day scheduling window exists to accommodate adverse weather, holidays, or other scheduling issues.

n. Beginning with Cycle 2 Day 1, the start of a subsequent cycle may be delayed by up to 7 days to accommodate vacations, holidays, or other scheduling issues. Enough study medication supply should be dispensed to participants to allow for any pre-planned scheduling delays.

o. Off treatment evaluation to be completed within 30 days of the last dose of study medication. Note: follow-up visits or other contact is required in order to identify SAEs during the 30 days following treatment.

p. Participants will be followed until death or withdrawal of consent after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks during the initial therapy phase of the trial, and then every 8 weeks thereafter. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

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

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with any of the protocol agents.

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

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area may not be considered measurable unless there has been demonstrated progression in the lesion.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan

slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

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

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

11.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one

assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

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

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false

positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

Investigator).

11.1.4.3 Evaluation of Best Overall Response

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

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

Table 22: For Patient with Measurable Disease (*i.e.*, Target Disease)				
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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

Table 23: For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD

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

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from randomization to time of progression or death, whichever occurs first. For the primary comparison regarding maintenance therapy, PFS is defined as the duration of time from the *second* randomization (to CO maintenance or no further therapy) for the subset of patients initially randomized to EP initial therapy who do not experience progressive disease. For the secondary comparisons regarding initial therapy, PFS is defined as the duration of time from the *first* randomization (to EP initial therapy or EPC initial therapy).

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

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

The protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. In addition, a conference call will be held after the first 10 participants are enrolled in the EPC arm to specifically review toxicity of the combination and determine whether there are unexpected adverse effects that should affect continued enrollment (specifically, if there are ≥4 grade 3 or above events, this should prompt re-evaluation of dosing for the combination. Following the interim analysis, a decision to proceed will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

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

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

12.2 Data Reporting

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

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

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

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be

submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11CTMSSupport@theradex.com. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

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

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

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

An End of Study CRF is to be completed by the PI, and is to include the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex

on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

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

12.3 CTEP Multicenter Guidelines

n/a

12.4 Collaborative Agreements Language

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

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

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

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

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

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must

agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

12.5 Genomic Data Sharing Plan

n/a

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a phase II randomized study of cisplatin/carboplatin plus etoposide (EP) ± cediranib followed by maintenance therapy with cediranib plus olaparib or no maintenance therapy. Patients will be randomized 2:1 to cisplatin/etoposide (EP) with or without cediranib (EPC) in initial therapy, with 2/3 of the patients randomized to initial therapy with EP alone. After initial therapy, patients with stable disease or better by RECIST version 1.1 criteria on EP alone will be randomized equally to no maintenance therapy or maintenance therapy with cediranib/olaparib (CO). Patients randomized to EPC as initial therapy will be directly assigned to receive maintenance therapy with cediranib/olaparib (CO).

The primary objective of the trial is to assess the median PFS (in months) in participants who receive CO as maintenance therapy compared to those receiving standard therapy (no maintenance treatment); this comparison will involve the subset of patients assigned to initial therapy with EP alone who do not experience progressive disease and are randomized to no maintenance therapy or CO maintenance therapy. PFS will be defined as the time from second randomization to documented disease progression or death from any cause, whichever occurs first. Patients who have not experienced an event of interest by the time of analysis will be censored at the date of the last disease assessment without progression. This analysis will use the intention-to-treat framework in which all patients randomized are considered recipients of their randomized assignment, regardless of treatment actually received.

The sample size for this study is driven so that there would be adequate power to address the primary question of randomized therapy in maintenance. We will randomize 120 eligible patients in a 2:1 ratio to EP and EPC initial therapy, resulting in 80 randomized to EP and 40 randomized to EPC. Assuming that 80% of all patients randomized to EP initial therapy will achieve a response or stable disease and thus be randomized to the maintenance therapy comparison, we expect 64 patients to undergo the second randomization. A total of 48 PFS events among these 64 patients will provide 87% power to detect a PFS hazard ratio of 0.5 with testing at the one-sided 0.10-level using a logrank test. Assuming exponential event times, this corresponds to an improvement in median PFS from 3 months to 6 months in the maintenance phase of therapy. It is possible that fewer than 80% of patients will be randomized in the maintenance (second) randomization, e.g., if fewer patients achieve a response or stable disease to the EP initial therapy. To avoid an extended time period for completion of this trial but minimize power loss, the definitive analysis will be performed when 48 PFS events have occurred or when 90% of the patients who participate in the maintenance (second) randomization have PFS events, whichever comes first. For example, if only 60% of patients registered to initial therapy are achieve PR/SD and are randomized to maintenance therapy (48 patients), then the analysis would be performed when there were 43 PFS events. This would provide power of 84% power to detect the hazard ratio of 0.5. Because we expect that approximately 10% of patients of enrolled patients will be ultimately ineligible or will not start assigned therapy, we will enroll 132 patients in order to randomize 120 in the first step.

As secondary analyses, it is also of interest assess the effect of EP vs EPC initial therapy. Two secondary comparisons are of interest, which will be include all participants randomized to initial therapy. The first compares those randomized to EP alone in the first randomization and no maintenance in the second randomization to those randomized to EPC in the first randomization followed by OC maintenance. That is, this comparison compares the standard of care to the maximal regimen. We anticipate that 120 eligible and treated patients will be randomized to EP vs EPC initial therapy, with 80 randomized to EP induction and 40 randomized to EPC initial therapy. The analysis will be done when there are 35 PFS events among the 40 patients randomized to EPC during initial therapy. (PFS here is measured from the first randomization) To account for the potential confounding effect of maintenance therapy in the analyses and comparisons of initial therapies, we will employ inverse-probability weighted Cox regression, (81-83) which will weight the information contributed by those randomized to maintenance observation after EP induction by approximately a factor of 2. This will maintain proper representation of patients who do and do not undergo the second randomization to maintenance therapy. The second randomization is used to determine the weighting factor in the proposed analysis methods. If the median PFS (from first randomization) is improved from 5.5 months in the EP initial therapy arm and no maintenance arm to 8.5 months with the EPC induction followed by OC arm, we would expect approximately 30 PFS events (among 32 patients randomized) in the EP initial therapy followed by no maintenance arm at the time of analysis (35 PFS events in the EPC initial therapy arm). This should provide roughly 70% power for this secondary comparison. We will plan to conduct sensitivity analyses to assess the impact of the weighting factor at the time of interim and final analysis.

The other secondary comparison compares those randomized to EP alone in the first randomization and OC maintenance in the second randomization to those randomized to EPC in the first randomization followed by OC maintenance. That is, this comparison isolates the effect of EPC vs EP initial therapy when followed by OC maintenance. The analysis will be performed analogously to the first secondary comparison. These secondary analyses assume a one-sided 10% level test.

Response rate will be analyzed as an additional secondary outcome. Rates in each arm will be provided with exact 95% confidence intervals, and compared using the chi-squared test (or Fisher's exact test, as needed). In addition, we will conduct exploratory analyses using biopsy tissue (see below) of predictive markers of response using logistic regression. In addition, we will conduct exploratory analyses using biopsy tissue (see below) of predictive markers of response using logistic regression.

Interim Analysis

This study will also be monitored for futility(84). For the primary maintenance question, an interim analysis at roughly 50% information (24 PFS events [measured from second randomization] for the primary maintenance question) is planned. At that time, if the point estimate of the PFS hazard ratio is consistent with detriment (HR > 1.0), then the

data monitoring committee may consider terminating the study early for overall lack of treatment difference between the two maintenance therapies. For the secondary induction questions, an interim analysis at roughly 50% information (16 PFS events observed in the EPC initial therapy arm [measured from first randomization] is planned. At that time, if the (weighted) point estimate of the PFS hazard ratio for either comparison is consistent with detriment (HR > 1.0) of the EPC initial therapy arm, then the data monitoring committee may consider terminating accrual to the EPC initial therapy arm.

13.2 Sample Size/Accrual Rate

Assuming roughly 10% of patients will not be eligible or start assigned therapy, a total of 132 patients would constitute the total sample size. Accrual time is estimated to be a total of 24 months, enrolling 2-4 patients per month across multiple sites. Participants will be followed for at least one year post therapy completion. The total study duration will be 36 months.

PLANNED ENROLLMENT REPORT

Table 24: Planned Enrollment Report

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	6	8	0	0	**14**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	4	5	1	2	**12**
White	43	51	4	6	**104**
More Than One Race	1	1	0	0	**2**
Total	**54**	**65**	**5**	**8**	**132**

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13.3 Stratification Factors

n/a

13.4 Analysis of Secondary Endpoints

Secondary efficacy measures will include analysis of cediranib plus olaparib on the OS rate in patients with SCLC. OS will be defined as the time from initial randomization to death from any cause. Patients who are thought to be alive at the time of final analysis will be censored at the date of last contact. Additional sensitivity analyses will be conducted on OS to address the effect of potential crossover to olaparib/cediranib on overall survival estimates. These will include rank preserving structural failure time models.

Safety and tolerability will be assessed using CTCAE version 5.0.

Exploratory evaluation of blood-based angiogenic and DNA repair biomarkers will be conducted from samples collected at time points specified in Section 9. WES will be performed on diagnostic biopsy samples and tumor-derived circulating free DNA (cfDNA) will be collected for WES as well. Data from correlative studies will be summarized using descriptive statistics.

Initial analyses of these data will utilize tests for association comparing the frequency of a particular genomic aberration at baseline and at progression (for example, using McNemar's test) and association between alterations and baseline characteristics (for example, using Fisher's exact test). More sophisticated analyses may include multivariable logistic regression modeling and/or competing risks analysis, however it is expected that analyzable results will not be obtained from 100% of patients (either due to things like assay failure, inability to biopsy at progression due to poor patient health, etc).

For the aims related to plasma genotyping and serial plasma collection, we may employ a variety of statistical techniques for the analyses of these data. The rate of change at a particular time point may be compared to baseline measures of cfDNA and that measure will be analyzed for association with patient demographics and/or disease characteristics using the Kruskal Wallis test. Landmark analyses of PFS and OS in which the landmark time is defined by the cfDNA measurements at a particular time point, may be used as well. Presence or absence of mutations in plasma will be analyzed for association with other variables using Fisher's exact test. To account for the repeated measures of plasma over time, we may potentially use these data as time varying covariates in multivariable Cox models to study their impact on outcomes like PFS and OS.

We anticipate 75% of patients to have archival/diagnostic tissue available and 50% to have adequate tissue for all planned analyses which are primarily to evaluate predictive markers of response (i.e. DNA repair score, PARP expression, blood-based cytokine profile, etc). We anticipate that we will obtain very few post-treatment optional biopsies for comparison to archival tissue (20% or less) but would be looking for changes in

PARP expression, levels of individual circulating cytokines (i.e. VEGF), or changes in genomic profile or gene expression profile that may identify a resistance mechanism. For these evaluations, descriptive statistics would be employed.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first dose of study medication. As noted in section 12.1 The Overall Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. In addition, a conference call will be held after the first 10 participants are enrolled in the EPC arm to specifically review toxicity of the combination and determine whether there are unexpected adverse effects that should affect continued enrollment (specifically, if there are ≥4 grade 3 or above events, this should prompt re-evaluation of dosing for the combination. All adverse events will be reported as in section 7.3.

13.5.2 Evaluation of Response

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

All of the participants who proceed to the second randomization (those who have partial response or stable disease after completion of initial therapy) should be included in the primary analysis of PFS from the time of second randomization. Participants who are randomized to initial therapy will also be included in the analysis of the secondary endpoints (comparing EP to EPC initial therapy (with or without maintenance)) as the intention-to-treat population. 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.

All conclusions will be based on all eligible participants (those who are able to be randomized to treatment). 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 will not serve as the basis for drawing conclusions concerning treatment efficacy

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78. Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.
79. 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.
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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B **PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD**

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **cediranib (AZD2171).** This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

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

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

June 2016

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

Cediranib (AZD2171) interacts with many drugs which can cause side effects. Because of this, it is very important to tell your study doctors about all of your medicines before you enroll on this clinical trial. It is also very important to tell them if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care prescribers can write prescriptions. You must also tell your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Cediranib (AZD2171) must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of FMO1, FMO3, UGT1A4 and P-gp." Cediranib (AZD2171) inhibits enzymes "CYP 2D6 and 3A4, transport proteins BCRP, P-gp, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K and is highly protein-bound." These characteristics may change how other medicine works in your body.

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

June 2016

STUDY DRUG INFORMATION WALLET CARD

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

- Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistant, nurse practitioners, pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Cediranib (AZD2171) interacts with CYP3A4, 2D6, FMO1, FMO3, UGT1A4 and transport proteins, P-gp and BCRP and must be used very carefully with other medicines that interact with these enzymes and proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered ""strong inducers/inhibitors of FMO1, FMO3, UGT1A4 and P-gp." Cediranib (AZD2171) inhibits "CYP 2D6 and 3A4 and transport proteins BCRP, P-gp, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K and is highly protein-bound." It may change how other medicine works in your body.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX C OLAPARIB PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **olaparib (AZD2281).** This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

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

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

November 2015

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

Olaparib may interact with many drugs which can cause side effects. Because of this, it is very important to tell your study doctors about all of your medicines before you enroll on this clinical trial. It is also very important to tell them if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care prescribers can write prescriptions. You must also tell your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Olaparib must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP3A4/5 and P-gp." Olaparib inhibits enzymes "CYP3A4, UGT1A1, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP." Olaparib possibly induces "CYP 1A2, 2B6, 3A4, 2C9, 2C19 and P-gp." These characteristics may change how other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit, grapefruit juice and Seville oranges while taking olaparib.
- You may need to be monitored more frequently if you are taking any drugs that have narrow therapeutic ranges.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

November 2015

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental drug **olaparib (AZD2281).** This clinical trial is sponsored by the NCI. Olaparib interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Olaparib interacts with liver enzymes, CYP3A4/5, 1A2, 2B6, 2C9, 2C19, UGT1A1, and transport proteins, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP.

- Olaparib must be used very carefully with other medicines that interact with these enzymes and proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered ""strong or moderate inducers/inhibitors of CYP3A4/5 and P-gp." Olaparib inhibits "CYP 3A4, UGT1A1 and transport proteins P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP and induces CYP 1A2, 2B6, 3A4, 2C9, 2C19 and transport protein P-gp." It may change how other medicine works in your body.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

APPENDIX D CONCOMITANT MEDICATIONS

The following tables list CYP3A4 inducers **(Table 25)** and inhibitors **(Table 26)**. Investigators should consult a frequently updated drug information reference for a list of strong inducers and inhibitors. Please refer to Section 5.3 for further detail on concomitant medications.

Table 21: CYP3A4 Inducers (Prohibited)

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

Table 22: CYP3A4 Inhibitors		
Strong Inhibitors (Prohibited)	**Moderate Inhibitors** (use with caution, avoid if possible)	**Weak Inhibitors** (use with caution, avoid if possible)
Amprenavir[1] Atazanavir[1] Clarithromycin Conivaptan[1] Delavirdine[1] Fosamprenavir[1] Fospropofol[1] Imatinib[1] Indinavir Isoniazid[1] Itraconazole Ketoconazole Miconazole[1] Nefazodone Nelfinavir Nicardipine[1] Posaconazole[1] Propofol[1] Quinidine[1] Ritonavir Saquinavir[2] Telithromycin	Amiodarone[1] Aprepitant Cimetidine[1] Clotrimazole[1] Cyclosporine[1] Desipramine[1] Doxycycline[1] Efavirenz[1] Erythromycin Fluconazole Fosaprepitant[1] Grapefruit juice Haloperidol[1] Lidocaine[1] Metronidazole[1] Norfloxacin[1] Sertraline[1] Tetracycline[1] Verapamil Voriconazole[1]	Chloramphenicol[2] Ciprofloxacin[2] Diethyldithiocarbamate[2] Fluvoxamine[2] Gestodene[2] Mibefradil[2] Mifepristone Norfluoxetine[2] Star fruit[2] Troleandomycin[2]

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

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

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

APPENDIX E CEDIRANIB AND OLAPARIB DRUG DIARY

Today's Date: _____ Cycle #: _____

Patient Name: Patient Study ID: _____

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

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

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

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

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

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

APPENDIX F CEDIRANIB DRUG DIARY

Today's Date: _____ Cycle #: _____

Patient Name:_____ Patient Study ID: _____

1. Complete one form for each cycle (21 days).
2. Record the date, the number of tablets you took, and when you took them.
3. Bring your pill bottles (including empty bottles) and this form to every appointment.
4. Do not chew, dissolve, or crush medications. DO NOT make up vomited doses.
5. If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose.
6. The first row in the table below is an EXAMPLE ROW for how to complete this diary.

CEDIRANIB

Take____ (number) ____mg tablets once a day. Take on an empty stomach (fast at least 2 hours before each dose and for 1 hour after each dose).

Day	Date	15mg	20mg	AM
1	*1/1/15*	*0*	*1*	*7:00*
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
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Patient's Signature: _____ Date: _____

Physician/Nurse/Data Manager's Signature_____ Date_____

APPENDIX G ORAL ANTIHYPERTENSIVE MEDICATIONS

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

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

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

APPENDIX H BLOOD PRESSURE DIARY

Today's Date: _____ Cycle #: _____

Patient Name:_____ Patient Study ID: _____

Instructions to the Patient:

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

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

Patient's Signature: _____ Date: _____

Physician's office will complete this section:

Date of this clinic visit _____

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

APPENDIX I DIARRHEA MANAGEMENT

Diarrhea is a common problem experienced by many patients and is a risk with olaparib, cediranib, and chemotherapy. If it is not controlled quickly, it can lead to dehydration.

WHEN TO REPORT YOUR DIARRHEA

- Fever 100.5° or higher with diarrhea.
- If you are experiencing diarrhea for the first time after starting therapy. Based on questions answered during that phone call, we will advise starting Imodium AD if it seems the symptoms are treatment-related
- are still have diarrhea 24 hours after starting Imodium AD—at this point, your doctor may advise additional prescription medications or want to evaluate you in person if there is a concern that you are becoming dehydrated

OVER THE COUNTER MEDICATION MANAGEMENT OF DIARRHEA:

- For diarrhea that occurs more than 2 episodes/day or more than one day continuously, use **Imodium AD** (maximum of 8 caplets per day) We recommend that you have Imodium AD on hand at home prior to starting therapy.
  - 1st dose: Take 2 caplets (4mg)
  - During the day: Take 1 caplet (2mg) every 2 hours after each loose stool
  - During the night: Take 2 caplets (4mg) at bedtime and every 4 hours as needed

DRINK PLENTY OF FLUIDS

- Drink 8 to 10 large glasses of liquids a day to replace those lost by diarrhea. Drink small quantities at a time slowly.
  - **Water** should only be part of the 8 to 10 glasses a day; it does not replace lost minerals
  - **Jello** is a good source of fluids
  - **Gatorade** replaces lost salt and potassium
  - **Clear soup** or **broth** replaces lost salt
  - **AVOID** caffeinated, very hot, or very cold drinks

EAT SMALL MEALS OFTEN

- A good choice of foods for diarrhea is the BRAT diet:
  - **B**- bananas- help replace lost nutrients
  - **R**- rice- easily digested and binding because it is a starch
  - **A**- apple sauce- provides sugars for energy
  - **T**- toast- easy to tolerate and binding because it is a starch
- When these foods are being well tolerated, then you can add other bland low fiber foods such as:
  - Foods easy to digest: chicken- white meat without the skin, steamed rice, crackers, white bread, pasta noodles without sauce, and canned or cooked fruits without skins
  - Foods high in potassium: bananas, apricots without skin, peach nectar, potatoes

without skin, broccoli, halibut, mushrooms, asparagus, non-fat milk

- Foods that can make diarrhea and cramping worse:
  - Fatty, fried, greasy, or spicy foods can cause more problems and discomfort
  - High-fiber foods: bran, whole grain cereals, dried fruit, fruit skins, popcorn, nuts and vegetables
  - Foods that cause gas: Beer, beans, cabbage, carbonated drinks