SUMMARY OF CHANGES -- Protocol

NCI Protocol #: 10067
Local Protocol #: 17-735
Protocol Version Date: 05/10/2019

Protocol Title: A randomized phase 2 trial of cediranib and olaparib compared to bevacizumab in patients with recurrent glioblastoma who have not received prior VEGF therapy.

I. Changes Requested by CTEP Request for Rapid Amendment (RRA) May 9, 2019

#	Section	Comments
1.	Title page and header	Updated protocol version date 05/10/2019

2.	7.1.1.1 CAEPR for Olaparib	• Increase in Risk Attribution:
		  • Changed to Less Likely from Also Reported on Olaparib 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."
		
		PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.4, and associated risk information for the ICD, to the most recent CAEPR Version 2.3. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.3), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

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Local Protocol #: 17-735

ClinicalTrials.gov Identifier: NCT02974621

TITLE: A randomized phase 2 trial of cediranib and olaparib compared to bevacizumab in patients with recurrent glioblastoma who have not received prior VEGF therapy.

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NCI-Supplied Agents:

Cediranib (NSC 732208)

Olaparib (NSC 747856)

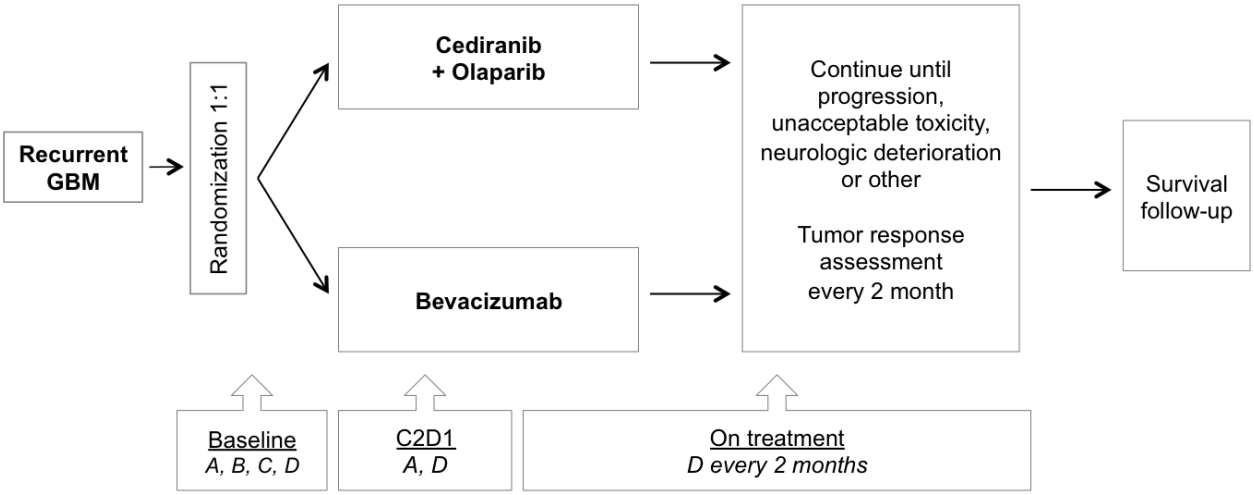
Other Agents:

Bevacizumab (NSC 704865), commercially supplied

IND Sponsor: *DCTD, NCI*

Protocol Type / Version / Version Date: Original / 15 / May 10, 2019

SCHEMA



A: Plasma cytokines for angiogenesis (Biomarker Review Committee-approved Plasma Angiome panel)
B: Tissue and blood biomarkers of DNA repair (Biomarker Review Committee-approved BROCA panel)
C: Whole exome sequencing of formalin-fixed paraffin embedded (FFPE) tissue
D: MRI brain (routine + perfusion, permeability and diffusion tensor imaging)

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1. OBJECTIVES

1.1 Primary Objectives

1. To compare the anitumor activity of cediranib/olaparib versus reference bevacizumab monotherapy, as measured by progression-free survival at 6 months (PF6), in patients with recurrent GBM.

1.2 Secondary Objectives

1. To compare overall survival (OS), progression free survival (PFS) and objective response (ORR) in patients with recurrent GBM treated with cediranib/olaparib versus bevacizumab
2. To assess the safety of the combination of olaparib and cediranib in patients with recurrent GBM
3. To evaluate the association of blood based biomarkers involved with angiogenesis using the Biomarker Review Committee-approved Plasma Angiome Panel (bFGF, Ang-1, Ang-2, Tie-2, SDF1-α, Collagen IV, PlGF, sVEGFR1, sVEGFR2, VEGF, Il-1β, Il-6, Il-8, TNF-α, CAIX) with the clinical activity of cediranib/olaparib.
4. To evaluate the association of tissue biomarkers involved with DNA repair using the Biomarker Review Committee-approved BROCA panel with the clinical activity of cediranib/olaparib.
5. To identify genomic alteration by whole exome sequencing in GBM tumor specimens that correlate with the clinical activity of cediranib/olaparib.
6. To evaluate the association of MRI imaging parameters (tumor perfusion and oxygenation, brain tumor cellularity) with the biological response of cediranib/olaparib.
7. To contribute genetic analysis data from de-identified biospecimens to Genomic Data Commons (GDC), a well annotated cancer molecular and clinical data repository, for current and future research; specimens will be annotated with key clinical data, including presentation, diagnosis, staging, summary treatment, and if possible, outcome
8. To bank formalin-fixed, paraffin-embedded (FFPE) tissue, blood (for cell-free DNA analysis), and nucleic acids obtained from patients at the ETCTN Biorepository at Nationwide Children's Hospital

2. BACKGROUND

2.1 Study Disease: Glioblastoma

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults with an incidence of two to three per 100,000 adults per year and accounts for 52% of all primary brain tumors. Despite recent advances in diagnosis and treatments, it typically results in death within

the first 15 months from diagnosis. Current standard of care for newly diagnosed GBM consists of maximal safe surgical resection followed by 60Gy radiotherapy with concurrent temozolomide, then 6 months of adjuvant temozolomide. Patients treated with this multi-modality therapy have a median survival of 14.6 months and a median progression free survival of 6.9 months (Stupp et al 2005). At the time of disease recurrence treatment options are limited and of poor effectiveness. Prior to the era of anti-angiogenic agents, single-agent irinotecan or nitrosoureas were used with an objective response rate of less than 10%, 6-month progression-free survival of 9-21% and median OS of 30 weeks or less (Friedman et al 2009, Batchelor et al 2013). More recently, bevacizumab, a monoclonal antibody that binds circulating vascular endothelial growth factor (VEGF) and prevents its interaction with VEGF receptors on cell surface, has been commonly used for recurrent GBM as its clinical activity was shown in phase II trials as a single agent or in combination with chemotherapy agents (Kreisl et al 2009, Friedman et al 2009, Taal et al 2014). In these trials, single-agent bevacizumab resulted in ORR of 28 - 38%, 6-month PFS of 16 - 57% and median OS of 31 - 36 weeks. These poor survival outcomes of recurrent GBM highlight urgent medical needs for new treatment strategies.

Like most proliferating tumors, GBM relies heavily on the accurate repair of double stranded breaks (DSB) and maintenance of genome stability, attributed in part to an intact homologous recombination (HR) pathway that works as a precisely regulated DNA lesion-specific repair mechanism (Santivasi, 2013). Importantly, dysfunction in repair of both single stranded breaks (SSB) and DSB would be synthetically lethal, making disruption of these repair mechanisms targets for treatment. The enzyme poly (ADP-ribose) Polymerase 1 (PARP) plays a key role in the repair of SSB, and PARP inhibitors have been successful in the treatment of cancers known to have HR deficiency, such as ovarian cancers and breast cancers with BRCA 1/2 mutations (Fong 2013, Fong 2010, Audeh 2010, Tutt 2010).

Recently, a significant extension of progression-free survival in patients with platinum-sensitive ovarian cancer was demonstrated with the combination treatment of an oral pan-VEGFR TKI, cediranib, with olaparib, an oral PARP inhibitor. Importantly, *post hoc* analysis suggested that cediranib plus olaparib could provide significant benefit even in the absence of BRCA 1/2 mutation. *In vitro*, hypoxia has been shown to down-regulate expression of HR repair gene, including BRCA 1/2 in both normal and cancer cells (Bindra 2005, Bindra 2004, Meng 2012) and to decrease the synthesis of HR proteins to offset chemo- and radio-resistance (Chan 2008). Moreover, tumor cells in the hypoxic and post-hypoxic periods show increased sensitivity to PARP inhibition (Klein 2010). VEGFR3 inhibition also results in down regulation of both BRCA 1 and 2 in cancer cells (Lim 2014). This suggests that angiogenesis blockade, perhaps through resulting hypoxia, could promote disruptions in the HR pathway such that patients without known HR deficiencies would benefit from PARP inhibition.

Loss of PTEN occurs in approximately 36% of GBMs. PTEN has nuclear functions including transcriptional regulation of the RAD51 gene, whose product is essential for HR (Shen 2007), and loss of PTEN has been shown to compromise HR-mediated repair in astrocytes (McEllin 2010). In GBM and other tumor cell lines, HR deficiency caused by PTEN loss sensitized tumor cells to PARP inhibitors, though notably there were effects on PTEN wild-type cells (Majuelos-Melguizo 2015, McEllin 2010). These data suggest that GBM may be sensitive to PARP

inhibition, but that induction of HR deficiency (by PTEN loss or hypoxia induction) may confer greater activity. It also suggests that patients with PTEN loss could have a greater response to the combination treatment with a PARP inhibitor and an anti-angiogenic agent.

GBM is further characterized by angiogenesis and up-regulation of multiple pro-angiogenic signal transduction pathways. Several pro-angiogenic cytokines play a role in tumor-related angiogenesis with VEGF playing a prominent role. Anti-VEGF therapies in the form of antibodies (for example, bevacizumab) and tyrosine kinase inhibitors (for example, cediranib) result in radiographic responses and extended progression free survival but have no demonstrated impact on overall survival in GBM patients (Batchelor et al 2013, Chinot et al 2014, Gilbert et al 2014). Bevacizumab received accelerated FDA approval as monotherapy for recurrent GBM in 2009. Several resistance mechanisms to anti-angiogenic therapies have been described and contribute to the failure of anti-VEGF therapy (Bergers 2008, Carmeliet 2011, Jain 2014). Importantly, the combination of PARP and VEGF inhibition targets multiple tumor pathways that may contribute to resistance, suggesting an alternate mode by which the combination of proposed therapies might potentiate each other's effects.

To date, studies on GBM and PARP inhibitors have focused on using these agents as radio- or chemo-potentiators. Several studies in GBM are being conducted combining PARP inhibitors with temozolomide to augment the pro-apototic effect of this methylating agent (NCT00687765, NCT02152982, NCT01390571) but results are pending. In the current phase 2 trial we will exploit the potentially synergistic action of PARP inhibition with anti-angiogenesis on DNA repair.

2.2 CTEP IND Agents

2.2.1 **Cediranib**

Cediranib (AZD2171, Recentin™; 4-[(4-fluoro-2-methyl-1*H*-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 (PO) -administered small molecule vascular endothelial growth factor (VEGF) receptor tyrosine kinase (TK) inhibitors with anti-angiogenic properties (Hennequin et al 1999; Wedge et al 2005).

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 (Hicklin and Ellis, 2005). Two high-affinity VEGF transmembrane receptors (VEGFRs) with associated TK activity have been identified on human vascular endothelium, VEGFR-1 (also known as fms-like tyrosine kinase 1 or Flt-1) and VEGFR-2 (also known as kinase insert domain-containing receptor or KDR) (Ferrara et al 2003). VEGFR-1 and VEGFR-2 signaling help mediate tumor progression. Cediranib has been developed as a potent inhibitor of VEGFR-1 and VEGFR-2 (Wedge et al 2005). Cediranib also has activity against VEGFR-3 and c-Kit (Jurgensmeier et al 2005). 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 Nonclinical Efficacy

The effect of cediranib was studied in athymic *nu/nu* mice bearing established subcutaneous human tumor xenografts of diverse histologies [SW620 (colon), PC-3(prostate), Calu-6 (lung), SKOV-3 (ovarian), and MDA-MB-231 (breast)]. Animals were administered cediranib PO at doses from 0.75-6 mg/kg/day (2.25-18 mg/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 (Drevs et al 2004). 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 RTK inhibitor 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 (Klinowska et al 2004). 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.

Further details of the nonclinical efficacy of cediranib can be found in the Cediranib Investigator's Brochure (2016).

2.2.1.3 Nonclinical Pharmacology and Toxicology

Nonclinical pharmacology and toxicology company-sponsored studies have been conducted in rats, dogs, and cynomolgus monkeys (Cediranib Investigator's Brochure, 2016). In rats and dogs, oral bioavailability is high, but absorption is relatively slow, with C_{max} 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 andintravenous (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 Investigator's Brochure, 2016). 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 nonclinical studies (Cediranib Investigator's Brochure, 2016). 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 (Cediranib Investigator's Brochure, 2011). 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.

Further details of the nonclinical pharmacology and toxicity of cediranib can be found in the Cediranib Investigator's Brochure (2016).

2.2.1.4 Clinical Pharmacology and Pharmacodynamics

Preliminary pharmacokinetics (PK) information indicates a time to maximum serum concentration (T_{max}) of 2 hours (range, 2-6 hours), a C_{max} of 107.8 ± 29.8 ng/mL, and a t1/2 of 12.1 ± 2.2 hours (Sridhar et al 2008). 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 (Batchelor et al 2010).

Additional information on the relationship between clinical outcome and biomarkers has been reported for a DCTD-sponsored trial (Sorensen et al 2009). Changes in vascular

permeability/flow as measured by magnetic resonance imaging (MRI) methods (K^{trans}), 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 reduction in K^{trans} after one dose of cediranib was seen in patients with increased PFS (*P*=0.0015) and overall survival (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 (Ramalingam et al 2008). A stark increase in CECs was noted at progression in several patients.

Further details of the clinical pharmacology and toxicity of cediranib can be found in the Cediranib Investigator's Brochure (2016).

2.2.1.5 Adverse Events and Recommended Dose

The most frequently reported AEs for cediranib on company-sponsored trials were fatigue, diarrhea, nausea, vomiting, hoarseness, hand-foot syndrome, and hypertension (Cediranib Investigator's Brochure, 2016). 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.

2.2.1.6 Clinical Experience

Cediranib is actively being investigated for use in patients with cancer. As of July 24, 2015, approximately 5800 patients have received cediranib through various phase 1-3 trials. There are no clinical studies with cediranib involving healthy volunteers. Details of the studies, responses, and safety assessments are summarized in the Cediranib Investigator's Brochure (2016).

Cediranib has been administered to patients in at least 38 DCTD, NCI-sponsored clinical trials. CRs and PRs have been reported in clinical trials of cediranib in solid tumors such as NSCLC (Gadgeel et al 2011), renal cell carcinoma (RCC) (Sridhar et al 2008), prostate (Dahut et al 2013), mesothelioma (Garland et al 2011), and gynecologic tumors (Hirte et al 2008; Matulonis et al 2009).

The 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 (Gerstner et al 2012). 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 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 (Batchelor et al 2010). Median PFS was 117 days, and median OS was 227 days. Additionally, cediranib alleviated brain edema, a major cause of morbidity in glioblastoma patients (Batchelor et al 2007). DLTs were observed in 9 of the 16 patients with hypertension; fatigue and diarrhea were seen most often.

In a randomised phase 3 study (REGAL) conducted in patients with recurrent GBM, clinical efficacy of cediranib monotherapy or in combination with lomustine, was compared with lomustine alone (Batchelor et al 2013). No significant difference was observed on PFS for the comparison of cediranib 30 mg versus lomustine alone, or for the comprison of cediranib 20 mg + lomustine versus lomustine alone. Furthermore, there was no differece in OS between the 3 arms. The incidence of SAEs was comparable between all 3 treatment arms. The most common SAEs (>4% of patients in any arm) reported during this study were thrombocytopenia, pulmonary embolism, neutropenia and convulsion. SAEs that occurred more frequently (by ≥2%) in the cediranib 20 mg + lomustine arm compared with the placebo + lomustine arm were thrombocytopenia, neutropenia, anaemia, pneumonia and convulsion.

Two phase 2 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 (Zhu et al 2012; Alberts et al 2012). Grade 3 AEs were observed in 93% of patients receiving 45 mg/day (Alberts et al 2012). 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 SD (Garland et al 2011). 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 (Matulonis et al 2009). 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 ≥3

(Robinson et al 2010). Grade 2 hypothyroidism occurred in 43% of patients.

ICON6 was a pivotal phase 3, multi-centre, 2-stage, randomised, 3-arm, double-blind, placebo-controlled study to determine the efficacy and safety of cediranib given in combination with platinum-based chemotherapy for 6 cycles followed by maintenance cediranib monotherapy in women with PSR ovarian cancer (epithelial ovarian, fallopian tube or serous primary peritoneal). There was a statistically significant improvement in PFS for the cediranib concurrent / maintenance arm (median 11.0 months) compared with the chemotherapy + placebo arm (median 8.7 months) with a HR of 0.57 (Raja et al., 2011).

Information on 59 patients in a trial of cediranib in metastatic androgen-independent prostate cancer has been reported (Dahut et al 2013). 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 (Sridhar et al 2008). 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 2 trial in small cell lung cancer (SCLC), in which one unconfirmed PR and eight SD were noted (Ramalingam et al 2008). 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 (Denduluri et al 2007).

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) (Gadgeel et al 2011). 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. Additional information on clinical trials conducted with cediranib is summarized in Lindsay et al

2009.

A phase III study evaluated cediranib 20 mg/day in combination with carboplatin/paclitaxel vs placebo in combination with carboplatin/paclitaxel, as first-line treatment, in patients with advanced NSCLC (Laurie et al 2014).

2.2.1.7 Safety Profile

As of August 2009, 582 patients on DCTD, NCI-sponsored clinical trials of cediranib had been evaluated for AEs. The most common grade 3/4 AEs were hypertension, fatigue, anorexia, diarrhea, and metabolic (ALT/SGPT and AST/SGOT).

Hypothyroidism was observed in 14/21 pediatric patients with CNS tumors administered cediranib, including one with a prolonged elevated TSH and thyroxine (T4) that went untreated. Proteinuria has been seen in seven patients, including two grade 3 events in Cycle 1 and Cycle 2, respectively. Hypertension has been observed in 18/21 patients who received more than a few days of therapy. Of the 18 cases, 10 experienced grade 2 hypertension as the highest reported grade and 8 reported grade 3 hypertension. Reversible posterior leukoencephalopathy syndrome (RPLS) shortly after initiation of Cycle 2 of therapy was seen in one patient who had been appropriately managed for grade 3 hypertension

In a phase 2 trial of cediranib in 46 patients with epithelial ovarian, fallopian tube, or peritoneal cancer, 31 patients (67%) developed hypertension by Day 3 of treatment, and 87% had developed hypertension by the end of the study (Robinson et al 2010). Fourteen women developed proteinuria, seven within the first 2 weeks of treatment. Only 7 of the 20 women who developed grade 3 hypertension developed proteinuria.

In a phase 2 study of cediranib in patients with solid tumors, patients (n=126) were assigned to cediranib dose groups of either 45 or 30 mg/day with or without antihypertensive prophylaxis (Langenberg et al 2009). Severe hypertension occurred in one patient receiving prophylaxis *versus* 18 in the non-prophylaxis groups.

Antihypertensive prophylaxis did not result in fewer dose reductions or interruptions. Increases in blood pressure, including moderate and severe readings of hypertension, were seen in all groups and successfully managed.

Hypertension and kidney toxicity (*i.e.,* proteinuria) are commonly observed AEs seen in the class of angiogenesis inhibitor agents (Izzedine et al 2007; Launay-Vacher and Deray, 2009). Indeed, many of the AEs observed in human clinical trials of cediranib have been described in studies of other angiogenesis inhibitors (Herbst, 2006; Kappers et al 2009). A number of mechanisms have been described that account for AEs such as impaired wound healing, gastrointestinal perforation, hemorrhage and thrombosis, cardiac impairment, endocrine dysfunction, and RPLS (Kamba et al 2007).

In a randomised double-blind phase III trial of cediranib (AZD2171) in relapsed platinum sensitive ovarian cancer (ICON6), diarrhea was one of the most commonly reported adverse reactions (93.0%). The majority of patients reported events of NCI CTCAE Grades 1 to 2 (74.0%), whereas NCI CTCAE Grade 3 diarrhea was less frequent (19.0%). Hospitalisations were infrequent (2.5%) and diarrhea led to cediranib discontinuation in 10.8% of patients. Although diarrhea was shown to have an early onset (within the first cycle), it can occur at any time during the treatment with cediranib. Dose pauses, and dose reduction, were frequently used to manage diarrhea (33.5% and 17.1%, respectively). In some patients dehydration (13.3%) and hypomagnesaemia (25.9%) were associated with diarrhea. Patients should be instructed to seek advice from their healthcare professional early.

2.2.2 **Olaparib (AZD2281)**

Olaparib (AZD2281, KU-0059436, CO-CE 42, 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one) is a potent and well-tolerated oral inhibitor of polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerization (PARP)-1 and PARP2. Olaparib is an active monotherapy in tumors with defective components of homologous recombination repair (HRR), which includes those with BRCA1/2 mutations. A first-in-man phase 1 dose escalation trial of single agent olaparib in a patient cohort enriched for patients with BRCA germline mutations indicated substantial PARP inhibition in surrogate tissues and anti-tumor activity in 40% of ovarian cancer patients with germline BRCA mutations, using combined RECIST and GCIG CA-125 criteria (Fong et al 2010).

2.2.2.1 Mechanism of Action

Preclinically, olaparib displays antitumor activity against a variety of tumor cell lines and this sensitivity of the cells is believed to depend upon components of a defective HRR capability (Olaparib Investigator's Brochure, 2013). As a major example of this selective activity, both BRCA1- and 2-deficient (-/-) tumors are sensitive to PARP inhibition. Early studies indicated that PARP inhibition in BRCA1/2 homozygous null cells, but not the isogenic BRCA heterozygous cells, led to cell death. BRCA1 and 2 are proteins necessary for proper function of HRR, the high fidelity repair system that addresses DNA double-strand breaks (DSBs). The backup repair system to HRR is base-excision repair (BER), which requires PARP function and primarily addresses single-strand breaks (SSBs). However, the system works both ways in that repair of SSBs in BER can lead to stalled replication forks that strain the system and cause double strand breaks, resulting in a situation that requires intact HRR and BRCA1 or BRCA2. Thus, HRR dysfunction sensitizes cells to PARP inhibition leading to further chromosomal instability, cell cycle arrest and apoptosis (Farmer et al 2005). This sensitivity is suggested to result in a large therapeutic window for PARP inhibition in mutation carriers. Pre-clinical studies support these findings showing that other BRCA mutant, but not wild-type, human cell lines are highly sensitive to olaparib (Menear et al 2008).

2.2.2.2 Nonclinical Pharmacology and Efficacy

Olaparib has demonstrated cellular activity in the low nM range with a cellular dose for 50% inhibition (IC50) of 2 nM in HeLa cells (Olaparib Investigator's Brochure, 2013). The effective concentration for inhibiting cellular PARP activity in cancer cells by >90% is approximately 30 nM to 100 nM olaparib in several tumor cell lines including ovarian A2780, breast MCF-7, and colorectal SW620. These concentrations lead to significant ablation of PARP activity (based on the inhibition of PAR formation), with maximal PARP-1 inhibition occurring at around 100 nM. Consistent with this, maximal potentiation of an appropriate DNA SSB-inducing chemotoxic agent (MMS) was also seen *in vitro* at 100 nM, which equates to 43.4 ng/mL.

An analysis of the correlation of olaparib response with several standard-of-care (SOC) chemotherapies in a panel of breast cancer cell lines has demonstrated a strong correlation with both carboplatin (0.84, p=0.0006) and camptothecin (0.8, p=0.0018) (Olaparib Investigator's Brochure, 2013). This is consistent with what is known about the types of DNA damage they induce (intra-strand and inter-strand cross-links for platinum and trapped topoisomerases-DNA adducts for camptothecins, both of which result in DNA DSB formation in replicating cells) and the DDR pathways that deal with them (primarily HRR in cells undergoing DNA replication). The same does not hold for a mechanistically unrelated chemotherapy, such as paclitaxel (-0.11) whose mechanism of action is unrelated to the induction of DNA damage.

The analysis of olaparib and platinum response was extended to additional tumor indications where platinum treatment is SOC and included ovarian, non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma cell lines (Olaparib Investigator's Brochure, 2013). Consistent with the breast cancer cell line data, the strong correlation between platinum response and olaparib response was observed. These *in vitro* data have been extended further into *in vivo* patient-derived tumor explant (PTX) models of both breast and NSCLC and again the correlation is seen between platinum sensitivity and olaparib sensitivity.

In vitro combination studies demonstrate that olaparib is able to potentiate the cytotoxicity of DNA-damaging agents, including the mono-methylating agent temozolomide (melanoma, glioblastoma, colorectal), topoisomerase-1 inhibitors such as camptothecin, irinotecan, and topotecan (ovarian, pancreatic, colorectal), and platinum-based agents such as cisplatin and carboplatin (breast) (Olaparib Investigator's Brochure, 2013). Studies with BRCA1-deficient orthotopically-transplanted *in vivo* mouse mammary tumor models showed that, in addition to single agent activity of olaparib, sequential treatment of mice with olaparib following a single dose of platinum agent increased the time to progression on treatment and extended OS. These data support the idea that olaparib can extend the antitumor effect of platinum agents when given as a maintenance treatment.

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

metabolism and elimination of foreign compounds. Further investigations are still ongoing. Excretion is primarily via the feces and, to a lesser extent, the urine.

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

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

In isolated human hepatocytes, olaparib was a substrate for organic anion transport proteins. In the same system, olaparib was shown to be an organic cation transporter 1 (OCT1) inhibitor (IC50 11.9 μM) (Olaparib Investigator's Brochure, 2013). In HEK-293 cells transfected with OATP1B1, olaparib functioned as an inhibitor and IC50 values of 20.3 mcM and 27.1 mcM were derived (substrate dependent). Using the criteria defined in the European Medicines Agency (EMA) guidelines on the investigations of drug interactions (EMA 2013), it is possible olaparib may precipitate an interaction via hepatic drug uptake transporters, particularly OCT1.

SimCYP population PK simulations of the separate effect of co-administration of itraconazole and rifampicin (clinically relevant CYP3A inhibitor and inducer, respectively) on olaparib PK in humans, when administered at the recommended human dose, were performed (Olaparib Investigator's Brochure, 2013). The itraconazole (200 mg twice daily [BID] x 7 days) simulation indicated olaparib (400 mg bd x 7 days) steady state C_{max} and area under the concentration-time curve (AUC) would increase by 2.8 and 3.5 fold, respectively. The rifampicin simulation (600 mg x 6 days) indicated olaparib (400 mg BID x 6 days) steady state C_{max} and AUC in the presence of rifampicin would be reduced to 33% and 29%, respectively, of the values in the absence of rifampicin.

2.2.2.3 Nonclinical Toxicology

Olaparib has been tested in dogs and rats (Olaparib Investigator's Brochure, 2013). There were no noted effects on the cardiovascular or respiratory parameters of an anesthesized dog or any

behavioral, autonomic, or motor effects in the rat. Toxicology studies indicate that the target organ of toxicity is the bone marrow. *Ex vivo* work has confirmed that olaparib is also active against human marrow. The cytotoxic effect becomes evident at a higher concentration than required to fully ablate PARP activity. 28-day dog and rat studies demonstrate a reversible myelotoxic effect that is mild to moderate. Platelets are first affected, followed by white blood cells. In 26-week repeat-dose studies in rats, doses were well-tolerated in male rats, with hematological effects and increased spleen weights observed at all dosages. In female rats, doses of 15 mg/kg/day resulted in significant reduction in body weight. Hematological effects and increased spleen weights were again observed at all dosages. The difference between sexes was considered to be due to the fact that females had greater plasma exposure levels than males. In 26-week repeat-dose studies in dogs, olaparib was well-tolerated. Hematological changes were observed, characterized by pancytopenia.

2.2.2.4 Clinical Pharmacology

Olaparib is rapidly absorbed following capsule oral dosing in cancer patients (Olaparib Investigator's Brochure, 2013). Mean volume of distribution was 40.3 L, mean plasma clearance was 4.55 L/h, and the estimated terminal half-life (t1/2) was between 5 and 12 hours. Exposure increased proportionally with dose at doses up to 100 mg but increased in a less than proportional fashion at higher doses. On multiple dosing, there was no evidence of time dependency of the PK and no marked accumulation. There was no evidence of ethnic difference in olaparib PK between Japanese and Caucasian patients. Recovery of administered radio-labelled olaparib dose was >94% in four patients and approximately 60% in a further two with the lower recoveries apparently due to slower fecal excretion of dosed material by these two patients. Drug-related material was eliminated in the urine (35-50%) and in the feces (12-60%) with 6-20% of the dosed material recovered in the urine as unchanged drug. Plasma concentrations of olaparib were similar to those of total radioactivity up to 6 or 8 hours after dosing but the profiles diverged thereafter indicating the presence of circulating metabolites. Metabolite identification in plasma and the excreta is ongoing.

Studies of the relative single-dose bioavailability of capsule vs. tablet formulations showed that at the two lower tablet doses, the C_{max} with the tablet formulation tended to be slightly higher and the AUC was similar (Olaparib Investigator's Brochure, 2013). However, at the highest tablet dose (250 mg), the exposure delivered by the tablet formulation (both C_{max} and AUC) was higher than that delivered by the 400 mg capsule. The tablet and the capsule formulations cannot therefore be considered to be bioequivalent. Further details regarding PK comparisons between the capsule and tablet formulations may be found in the 2013 Olaparib Investigator's Brochure.

Table 2-1. Systemic Exposure of Olaparib Tablet vs. Capsule Formulations			
Parameter	**25 mg tablet vs. 50 mg capsule**	**50 mg tablet vs. 100 mg capsule**	**250 mg tablet vs. 400 mg capsule**
C_{max} ratio 90% CI	1.29 1.10 - 1.52	1.53 1.11 - 2.11	2.49 1.87 - 3.31
AUC ratio 90% CI	1.03 0.85 - 1.24	0.99 0.69 - 1.42	1.74 1.36 - 2.23

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

2.2.2.5 Clinical Efficacy

The first clinical study in man of olaparib (KU-36-92) was a dose-escalation study in patients with advanced solid tumors (Olaparib Investigator's Brochure, 2013). Preliminary data demonstrated that olaparib is generally well-tolerated at doses up to and including the MTD of 400 mg BID in patients with various solid tumors. As of October 2, 2013, approximately 2103 patients with ovarian, breast, pancreatic, melanoma, and other advanced solid tumors have received olaparib, either as monotherapy or in combination with other chemotherapy agents. AEs considered to be associated with olaparib included anemia (mild to moderate), neutropenia (mild to moderate), and thrombocytopenia (generally mild to moderate, sometimes severe), nausea and vomiting (mild to moderate), and fatigue (mild to moderate).

Olaparib has also been studied in an expansion phase in BRCA-deficient ovarian cancer at a dose of 200 mg BID. Fifty patients were treated, including 48 with BRCA-deficient germline mutations and two patients of unknown status or significance. Twenty (40%) patients achieved complete response (CR) or partial response (PR) by RECIST and/or GCIG-CA125 criteria. An additional three patients experienced stable disease (SD) for more than four cycles (Fong et al 2010). A multicenter phase 2 study enrolled two sequential cohorts of women with known germline BRCA2 or BRCA2 mutations and recurrent advanced ovarian cancer to receive olaparib continuously at a dose of 400 mg BID (Cohort 1) or 100 mg BID (Cohort 2) (Audeh et al 2010). Responses were observed in 33% (11 of 33) patients enrolled in the 400mg BID cohort and 13% (3 of 24) patients enrolled in the 100 mg BID cohort. A phase 2 study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer included a cohort of 46 ovarian cancer patients who were known not to carry a germline BRCA mutation, in which an overall response rate (ORR) of 23.9% was observed (Gelmon et al 2010).

Additional studies of olaparib as monotherapy or in combination with a platinum reagent for treatment of metastatic BRCA-deficient ovarian cancer are ongoing. Results from a phase 2 trial investigating olaparib as maintenance therapy following platinum-based therapy for platinum-sensitive serous ovarian cancer demonstrated a significant progression-free survival (PFS) benefit (8.4 vs. 4.8 months, $P<0.001$), with subgroup analyses demonstrating evidence of benefit regardless of BRCA status (Ledermann et al 2012). Lee and Kohn and colleagues have examined olaparib with carboplatin in two schedules in BRCA1/2 mutation carriers with breast and/or ovarian cancer and women with high grade serous ovarian cancers (Lee et al 2011). They also see activity with over 80% of ovarian cancer patients attaining either SD or PR lasting up to 18+

months. Additional phase 1 and 2 trials in both BRCA-deficient and BRCA-competent ovarian cancer are currently ongoing.

Olaparib was granted accelerated approved by the FDA in the United States as monotherapy in women with advanced ovarian cancer associated with germline BRCA mutation in the companion diagnostic test BRACAnalysis CDx and who have received at least 3 prior lines of therapy for ovarian cancer on December 19, 2014.

2.2.3 **Pre-clinical rationale for combination of cediranib and olaparib**

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, resulting in p53 accumulation and eventual apoptosis; p53-deficient tumors suppressed the apoptotic effect, promoting tumor survival in spite of the hypoxic state (Graeber et al 1996). However, despite the presence of DSB markers such as histone γH2AX, there is little evidence of DNA damage during the hypoxic state, and γH2AX staining is atypical (diffuse rather than punctate), though severe hypoxia may result in aberrant replication complexes, SSBs, and regions of single-stranded DNA (Hammond et al 2002). After re-oxygenation, DSBs are noted to accumulate, and tumor survival is dependent upon intact DNA repair complexes (Hammond et al 2004). 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 down-regulation (Bindra et al 2004; Bindra et al 2005). 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 (Hegan et al 2010). Exposure to PARP inhibitors or PARP-1 RNAi down-regulated BRCA1 and RAD51 expression in a dose-dependent manner, regardless of oxygenation, and the addition of hypoxic conditions to PARP inhibition enhanced the down-regulatory 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, γH2AX 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 γH2AX foci (Economopoulou et al 2009). 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 γH2AX formation, and siRNA knockdown of γH2AX 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* (Tentori et al 2007). 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 1α (HIF-1α) induction by the hypoxia mimetic agent $CoCl_2$, indicating that PARP inhibition's effects on migration were not exerted through influencing HIF-1α function.
Collectively, the evidence indicates that anti-angiogenic therapy may complement PARP inhibition, particularly in the context of DNA repair-deficient tumors. These results 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.

2.2.3.1 Nonclinical Efficacy

Limited nonclinical data exist regarding the specific combination of olaparib and cediranib. Olaparib (100 nM) and cediranib (5 nM) have potentially synergistic activity in *in vitro* microvascular cell tube growth assays (Figure 1), inhibiting cell tube growth and branching in a greater than additive fashion (Jung Min Lee, unpublished data) Olaparib (10 nM) and cediranib (50 nM) individually reduced tumor cell invasion, and the combination of both agents nearly completely abolished invasion compared to the control (Figure 2).

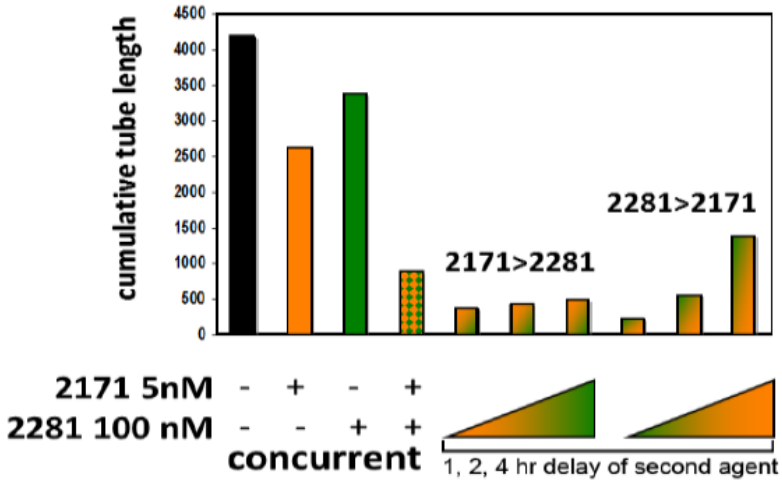

Figure 1. Microvascular cell tube formation assay.

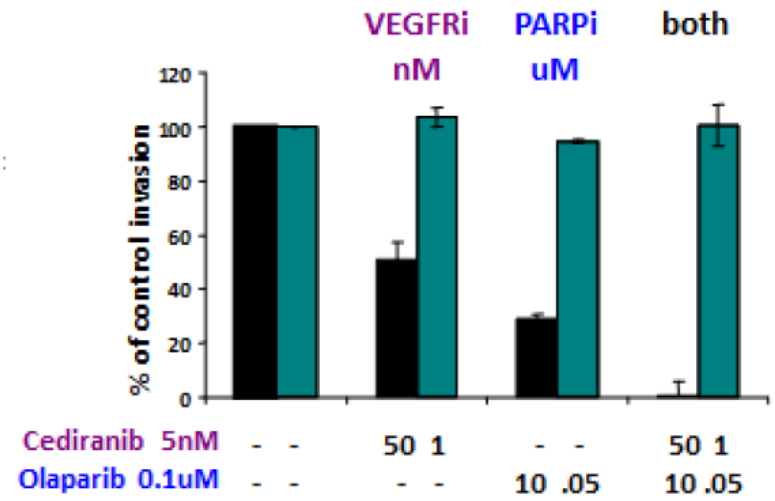

Figure 2. Tumor invasiveness assay.

2.2.4 **Clinical background for combination of cediranib and olaparib**

2.2.4.1 Phase 1 experience with cediranib and olaparib

NCI protocol 8348 included a Phase 1 component that established the recommended Phase 2 dosing (RP2D) of cediranib in combination with olaparib in the capsule formulation. This Phase 1 enrolled a total of 28 patients (20 ovarian, 8 breast). (Liu et al 2013)

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 recommended phase 2 dose (RP2D) was declared to be cediranib 30 mg QD and olaparib 200 mg BID (Liu et al 2013). 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 Response Evaluation In Solid Tumors (RECIST) criteria, version 1.1 (Liu et al 2013). 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 1-T component. Six doses of cediranib and olaparib tablets were explored (number of patients on each dose level in parentheses):

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

Three DLTs were observed across all patients enrolled to 8348 Phase 1-T; one DLT in the six patients on cediranib 30mg/olaparib 200mg, and two DLTs in the two patients on cediranib 30mg/olaparib 250mg. The recommended phase 2/3 dosing was therefore concluded to be cediranib 20mg daily and olaparib tablets 300mg BID or cediranib 30mg daily and olaparib tablets 200mg 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 20mg/olaparib 300mg dosing and one CR and two PRs in the six patients on the cediranib 30mg/olaparib 200mg dosing. To preserve uniformity of cediranib dosing with prior clinical trial experience, the dose of cediranib 30mg daily and olaparib tablet 200mg BID will be further explored in this study.

2.2.4.2 Phase 2 experience with cediranib and olaparib combination

A multi-center open-label randomized Phase 2 trial comparing the activity of the cediranib and olaparib combination to olaparib alone in platinum-sensitive recurrent ovarian cancer randomized 90 patients in a 1:1 ratio to either the combination or single agent olaparib (capsule formulation) (Liu et al 2014). Eligibility criteria for this trial included platinum-sensitive disease recurrence, with platinum-sensitivity defined as recurrence occurring greater than or equal to 6 months after the last platinum-containing regimen. Patients were allowed to receive an unlimited number of platinum-based lines of therapy, and up to one non-platinum-based regimen in the recurrent setting. No anti-angiogenics in the recurrent setting were allowed; no prior PARP-inhibitors were allowed.

The combination of cediranib and olaparib significantly extended both PFS and overall response rate (ORR) compared to olaparib alone in this patient population, with a median PFS of 9.0 months for olaparib alone and 17.7 months for cediranib/olaparib (HR 0.418, 95% CI 0.229-0.763, p = 0.005) (Figure 3). There were 2 complete responses (CR) and 20 partial responses (PR) in patients on olaparib alone (48% ORR) and 5 CRs and 30 PRs in patients on

cediranib/olaparib (80% ORR, p = 0.002).

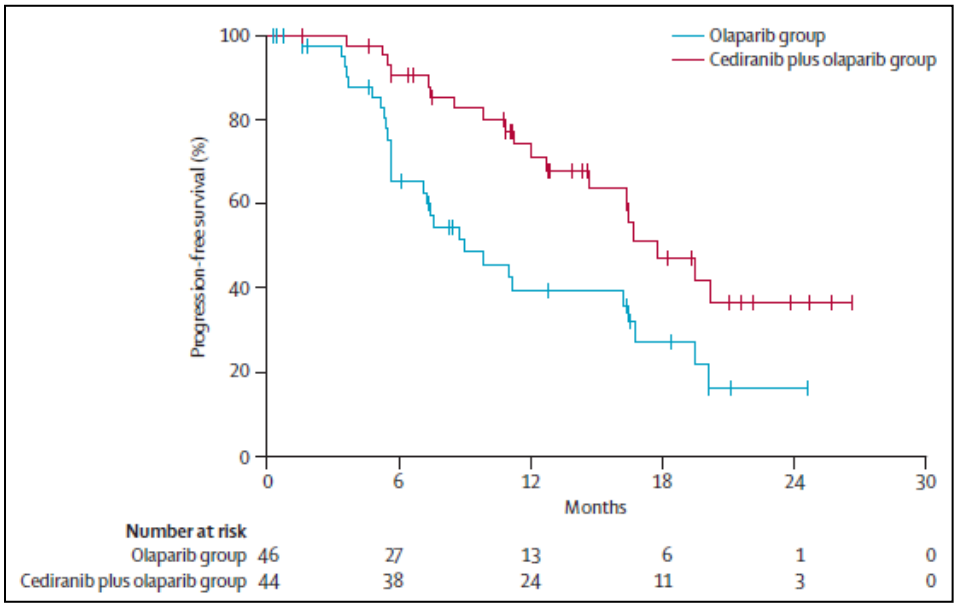

Figure 3. Kaplan-Meier PFS curves in patients treated on olaparib and cediranib/olaparib in Phase 2 trial.

Forty-seven of the 90 patients enrolled to the Phase 2 cediranib/olaparib vs. olaparib trial were known BRCA mutation carriers (25 olaparib; 23 cediranib/olaparib). A post-hoc subset analysis of PFS by BRCA mutation status (carrier vs. non-carrier/unknown) is shown in Figure 4. In BRCA mutation carriers, the median PFS was 16.5 months on the olaparib alone arm and 19.4 months on the cediranib/olaparib arm (HR 0.55, 95% CI 0.24-1.27, p = 0.16). In BRCA non-carrier/unknown patients, the median PFS was 5.7 months on the olaparib alone arm, and 16.5 months in the cediranib/olaparib arm (HR 0.32, 95% CI 0.14-0.74, p = 0.008).

Differentially occurring grade 3 or 4 toxicities attributed to study treatment included fatigue (27% cediranib/olaparib vs 11% olaparib, p = 0.06), diarrhea (23% vs 0%, p = 0.0004), and hypertension (41% vs 0%, p < 0.0001). There were two Grade 4 events, both in the cediranib/olaparib arm: 1 grade 4 hypertension in a patient who was not fully compliant with blood pressure monitoring and 1 grade 4 myelodysplastic syndrome (MDS). The patient with MDS had two prior lines of therapy and had been on study for approximately 1 year when she was diagnosed with MDS. Four patients on the cediranib/olaparib arm withdrew from study treatment secondary to toxicity (1 each due to weight loss, MDS, recurrent avascular necrosis in the setting of prior history of avascular necrosis, and vaginal fistula formation). Otherwise, AEs were manageable with a combination of symptom management and dose holds and/or reductions, and removal from the study for reasons other than a PFS event was balanced between the arms (2 withdrawal of consent, 1 investigator decision, 5 clinical progressions on cediranib/olaparib vs. 3 withdrawal of consent, 1 investigator decision, and 6 clinical progressions on olaparib alone).

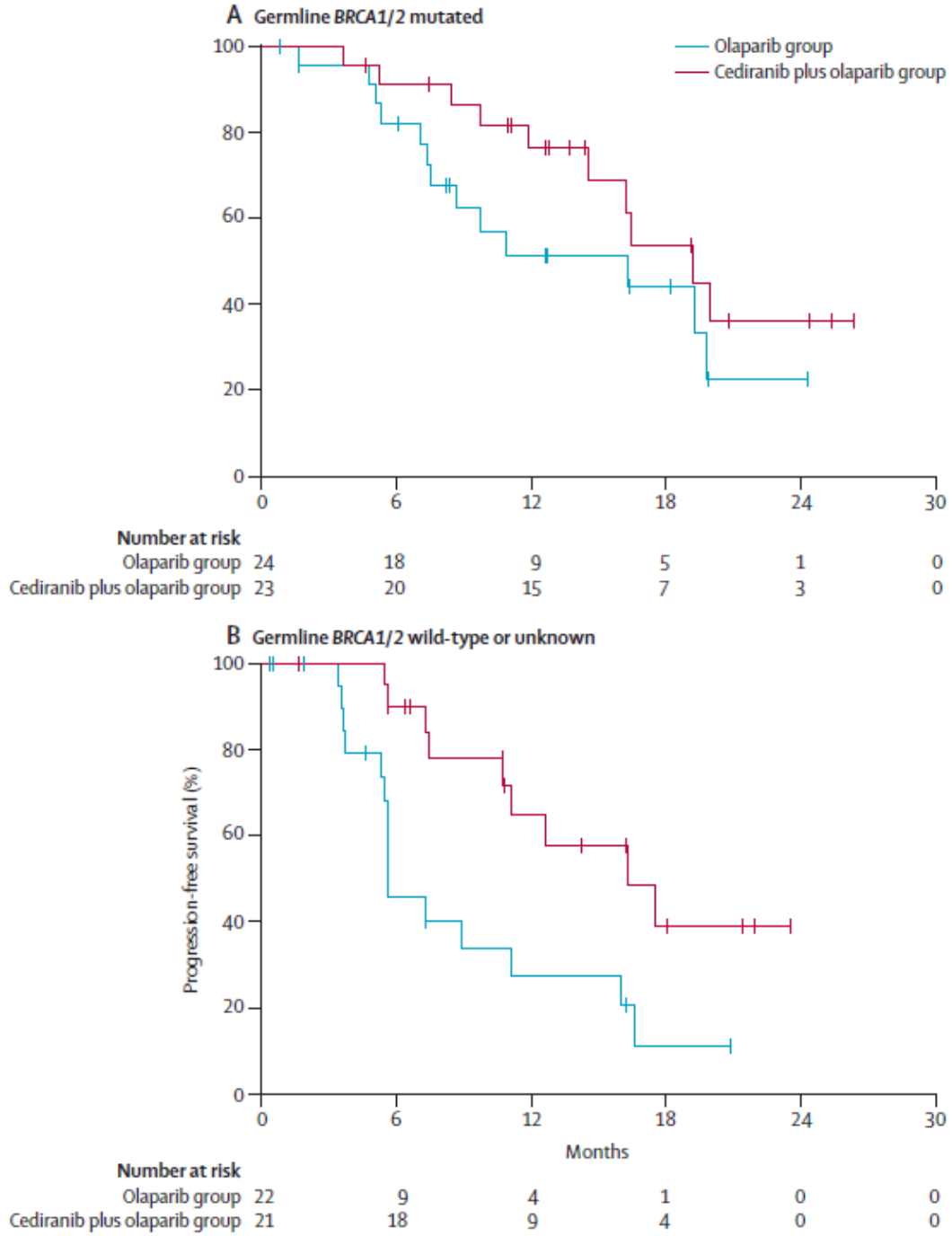

Figure 4. Kaplan-Meier PFS curves in BRCA mutation and BRCA non-carrier/unknown patients.

2.3 Advanced Imaging

2.3.1 MRI

Our goal is to explore changes in tumor vasculature resulting from treatment with Cediranib and olaparib and the impact these changes have on response to treatment. Results from this study will shed light on the potential mechanism of actions of cediranib and olaparib and how these agents may modulate tumor vasculature. This study will evaluate patients with recurrent glioblastoma with MRI to assess changes in tumor blood flow, blood volume, and vessel caliber, with advanced MRI.

Of note, this study will be run through the ECTCN across various sites. We anticipate that not all sites will have the capacity to perform some of the more sophisticated/advanced MRI sequences and, thus, may not participate in this exploratory aim of the study. We will assess feasibility across sites and if there is insufficient participation to the advanced MR portions of the imaging study, we will proceed with the standard MRI imaging only. Please refer to Appendix F for advanced imaging and stadard imaging protocols.

2.3.1.1 Rationale for use MRI

The dependence of tumor growth and metastasis on angiogenesis — which has been extensively demonstrated in animal models — has provided a powerful rationale for anti-angiogenic approaches to cancer therapy (van de Beek, 2007; Carmeliet & Jain, 2000; Kleihues et al 1993). Targeting blood vessels in brain tumors has been a particularly attractive strategy, given the characteristic high degree of endothelial proliferation, vascular permeability, and pro-angiogenic growth-factor expression (for example, VEGF) (Dvorak, 2002; Sundberg, 2001). The approval of bevacizumab, which neutralizes VEGF, in May 2009 for recurrent glioblastoma (rGBM) represented the first new therapy for this disease in many years. A strong antiedema effect is clearly seen with anti-VEGF therapy in many patients. Whether this conveys a survival benefit in subset of patients remains unknown; cediranib monotherapy did not improve survival over lomustine in rGBM in a recent phase III trial.

Bevacizumab and other anti-VEGF inhibitors are not an effective monotherapy outside the brain, but it is effective when combined with other drugs. The mechanism of this clinical efficacy is still incompletely understood. Anti-VEGF therapies have been shown to promote vascular “normalization” (Batchelor et al 2007; Jain et al 2005; Willett et al 2004) in many patients, which could improve local tumor blood flow and therefore cytotoxic chemotherapy delivery to the tumor. We have shown that the ‘normalization window’ of the anti-VEGF agent cediranib can be detected using serial, non-invasive MRI techniques in rGBM (Batchelor et al 2007), and we have seen increases in blood flow (Sorensen et al 2012). Whether this effect is similar with the combination of olaparib plus cediranib is unknown, and how oxygenation is affected also remains an outstanding question.

The acquisition of MRI should allow us to assess both hypoxia and vascular changes to determine the time course and interplay between vascular physiology, tumor oxygenation and response to treatment.

2.4 Bevacizumab

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human VEGF (or VEGF-A) with high affinity (kd = 1.1 nM). The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1.16-18. For this study, we will use the commercially available formulation of bevacizumab, Avastin.

2.4.1 Clinical Trials

Bevacizumab has been studied in multiple Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. In addition, data are available from 3,863 patients enrolled in two postmarketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date. The maximum tolerated dose of bevacizumab has not been determined; however, the dose level of 20 mg/kg was associated with severe headaches (Kim et al 1999). The dose schedule of either 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks is used in most phase II or III trials with only a few exceptions (e.g., the pivotal phase III trial in colorectal cancer, in which bevacizumab was given at 5 mg/kg every 2 weeks).

Clinical proof of principle for anti-VEGF therapy with bevacizumab has been provided by the pivotal phase III trial of bevacizumab (5 mg/kg every 2 weeks) in combination with bolus irinotecan/5-fluorouracil/leucovorin (IFL) in patients with untreated advanced colorectal cancer (AVF2107g) (Hurwitz et al 2004). In that study, the addition of bevacizumab to IFL was associated with an increase in objective responses (45% vs. 35%) and significant prolongations of both time to progression (10.6 vs. 6.2 months) and overall survival (20.3 vs. 15.6 months) compared with IFL. Based on the survival advantage, bevacizumab was approved in 2004 in the United States for first-line treatment in combination with IV 5-FU−based chemotherapy for subjects with metastatic colorectal cancer.

Additional data from Phase III trials in metastatic CRC (E3200), non−small cell lung cancer (NSCLC; E4599), and metastatic breast cancer (E2100) have also demonstrated clinical benefit from bevacizumab when added to chemotherapy (see the Bevacizumab Investigator Brochure for additional details). Additional clinical trials are ongoing in a variety of solid tumors and hematologic malignancies using bevacizumab as monotherapy or in combination with chemotherapy, radiation, or other targeted/biologic agents.

2.4.2 Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF) primarily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) (Ozcan et al 2006; Glusker 2006). There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-CTC Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome) Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose. Proteinuria will be monitored by urine protein : creatinine (UPC) ratio or urine dipstick at least every 2 weeks.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with

bevacizumab in the colorectal cancer trials, the recurrent glioblastoma trial and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials. Venous thromboembolic events (VTE) have also been observed in trials with bevacizumab and glioblastoma. In clinical trials across all indications the overall incidence of VTE events was 2.8%−17.3% in the bevacizumab-containing arms compared with 3.2%−15.6% in the chemotherapy control arms. Since VTE are very common in GBM independent of treatment (Stupp et al 2005), a relationship of VTE to bevacizumab in this population will be uncertain.

The first incidence of VTE will therefore not constitute a DLT. An increased incidence of arterial thromboembolic events (ATE) was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE include cerebrovascula accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE was 3.8% (37 of 963) in patients who received chemotherapy + bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy + bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy + bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy + bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

Gastrointestinal perforation: Patients may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and steroids or chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%−1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g. tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with

5- FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone. Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin or restart bevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that bevacizumab be restarted no earlier than 4 weeks after surgery).

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (Bevacizumab Investigator Brochure). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-Associated Hemorrhage: Major hemorrhage has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor associated hemorrhages. Tumor-associated hemorrhages were only very rarely seen in patients with high grade gliomas (1-2 %) (Cloughsey et al 2008).

Mucocutaneous Hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCICTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Reversible Posterior Leukoencephalopathy Syndrome: There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known.

Congestive heart failure: In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240−360 mg/m2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy (Miller et al. 2005). No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II−IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Additional Adverse Events: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

2.5 Rationale

The combination of cediranib and olaparib may offer a novel treatment regimen for patients with recurrent GBM whose current standard of care is single-agent bevacizumab. However, unanswered questions exist regarding the activity of the combination therapy in this clinical setting, and the biomarkers that may predict for tumor response to this regimen.

In this phase 2 trial, the potentially synergistic action of PARP inhibition and anti-angiogenesis on DNA repair and biomarkers of angiogenesis and DNA repair will be evaluated. Patients with recurrent GBM will be randomized to either the combination of cediranib plus olaparib or singe-agent bevacizumab. This will allow comparison of clinical anti-tumor activity of the combination therapy to that of bevacizumab.

Cediranib and olaparib have been tolerated in human studies and have limited significant overlapping toxicities, particularly when proactively managed (Liu 2014). Safety profiles of the combination will be assessed in patients with recurrent GBM.

2.6 Correlative Studies Background

2.6.1 Plasma Angiome

Currently there is no known biomarker that might predict for a response to the cediranib plus olaparib combination. To identify blood-based markers of anti-angiogenic inhibition, the Duke multiplex ELISA-based plasma angiome panel will be tested. This panel consists of a number of angiogenic biomarkers (Table 2.2, including Ang-2, stromal cell-derived factor (SDF)-1, VEGF-D, osteopontin (OPN), and interleukin (IL)-6. In order to develop the most optimal arrays, the Duke team leverages three multiplex protein array systems. Many analytes have been previously validated on the CiraScan platform, produced by Aushon Biosystems. Additional multiplex

systems that will be employed include the Meso Scale Discovery (MSD) and ProteinSimple platforms. The ProteinSimple platform uses microcapillary flow cells for improved sensitivity and reproducibility versus traditional ELISA techniques.

We have devoted considerable effort to the development and optimization of an appropriately designed panel for the evaluation key angiogenic and inflammatory markers. Table 2.2 below lists the panel of markers currently optimized; however, modifications to this list may occur based on the needs for any given study. This "Angiome" multiplex array has recently been approved by the NCI Biomarker Review Committee (BRC) as an integrated biomarker for use in two Phase III studies of cediranib and olaparib in both platinum-sensitive and platinum-resistant ovarian cancer. We worked closely with the NCI in developing our validation approach, establishing the key analytic features for protein multiplex array analyses. The Angiome multiplex array has gone through a rigorous evaluation to ensure data quality.

Recently, the approach was used to identify several strong candidate predictors of benefit from bevacizumab, including VEGF-D in CALGB80303 (Nixon 2013) and IL-6 in CALGB90206 (Nixon 2013). Studies are underway in ovarian cancer to investigate the utility of this plasma angiome panel in directing treatment with bevacizumab and with the cediranib/olaparib combination.

Table 2-2. Plasma-based marker identification

Soluble Angiogenic Factors		**Matrix-derived Factors**	**Markers of Vascular Activation and Inflammation**
ANG-2	VEGF-A	BMP-9	CD73
bFGF	VEGF-C	OPN	ICAM-1
HGF	VEGF-D	TGFβ1	IL-6
PDGF-AA	sVEGFR1	TGFβ2	IL-6R
PDGF-BB	sVEGFR2	TGFβR3	IL-6ST (GP130)
PlGF	sVEGFR3	TIMP1	SDF-1
		TSP2	VCAM-1

This approach is technically robust and readily adaptable to clinical practice. Because this data will be derived from patients, even preliminary data may significantly improve our understanding of how angiogenesis and tumor growth factors are regulated in cancer patients. Promising findings can be followed up in future clinical studies and in preclinical models. Because the Duke angiome lab serves as the core lab for multiplex ELISA analyses within the Alliance, the current ovarian cancer profiling can be compared to the profiles seen in other phase III studies, helping to optimize future profiling approaches and provide the disease specific context needed for clinically meaningful companion diagnostics. Given the results of this prior work and the work of others, we anticipate being able to identify and validate or refute candidate markers of benefit that are specific for anti-angiogenic agents.

2.6.2 **Biomarker Review Committee-approved BROCA panel**

BROCA is a targeted massively parallel sequencing assay that is capable of identifying all classes of mutations including gene rearrangements. This panel, performed at the University of Washington under the direction of Dr. Elizabeth Swisher, will be used to screen for abnormalities in a variety of genes that might be involved in DNA repair and may impact the activity of olaparib and cediranib in GBM. The goal of this assay is to determine if underling mutations in the tumor reflect a sensitivity or resistance to the olaparib/cediranib. Including it in the other arm will shed light on variations that may be treatment specific.

The University of Washington group has previously published the methodology and validation experiments for targeted capture and massively parallel sequencing of cancer genes (Nord et al 2011; Walsh et al 2011; Walsh et al 2010; Pritchard et al 2012; Pennington et al 2012).

The new version of BROCA (BROCA-HR) includes many additional DNA repair genes (75 total genes) as well as 3000 single nucleotide polymorphisms (SNPs). Similar sequencing accuracy and sensitivity sequencing DNA is obtained from formalin fixed paraffin embedded (FFPE), fresh blood and flash frozen specimens. BROCA-HR includes genes that are targets of both somatic and germline mutations. The BROCA-HR includes genes that regulate homologous recombination or NHEJ that, if mutated, could mediate resistance to PARPi such as *TP53BP1* (Johnson et al 2013; Bunting et al 2010; Bouwman et al 2010). The BROCA design is flexible and can be altered to include any genes of research interest. The current design for BROCA-HR includes the following genes:

BROCA-HR gene list (n=82)
a. BRCA-FA homologous recombination pathway: *ATM, ATR, BABAM, BAP1, BARD1, BLM, BRCA1, BRCA2 (FANCD1), BRCC3, BRE, BRIP1 (FANCJ), CHEK1, CHEK2, ERCC1, ERCC4 (FANCQ), FAM175A (abraxas), FANCA,FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG (XRCCC9), FANCI, FANCL, FANCM, GEN1, MRE11, NBN, PALB2 (FANCO), RAD50, RAD51, RAD51C (FANCO), RAD51D, RBBP8 (CtIP), RECQL, SLX4 (FANCP), UIMC1 (RAP80), XRCC2,*
b. DNA mismatch repair (Lynch syndrome) *MLH1, MSH2 (*and *EPCAM), MSH6, PMS2*
c. Other DNA repair or surveillance genes : *CDH4, CDK12, DDB1, HELQ, ID4, NEIL1, PPM1D, POLD1, POLE, RIF1, PARP1, PAXIP1, POLQ, RINT1, TP53, TP53BP1, USP28, WRN, XRCC3*
d. NER genes: *ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, DDB1, XPA, XPC,*
e. NHEJ pathway genes*: DCLRE1C, LIG4, PARP1, PRKDC, TOPBP1, XRCC4, XRCC5, XRCC6*
f. PI3K pathway: *PTEN, PIK3CA*

2.6.3 **Whole exome sequencing (WES)**

A goal of this study is to obtain archived tissue and blood specimens from patients enrolled to

ETCTN clinical trials for *WES.* Patient specimens will be analyzed to identify tumor mutations, amplifications, or translocations that may inform about the disease or about drug treatment mechanism of action, potential prediction of response, and interrogation of mechanisms of primary or secondary resistance to treatment in the early cancer drug development environment. Such profiling may also have predictive or prognostic import.

Archived tumor specimes and blood draw will be obtained from patients who sign the informed consent document to enroll in this treatment trial.

Whole exome sequencing of formalin-fixed paraffin embedded (FFPE) tissue will be performed at the Molecular Characterization Laboratory on the purified DNA and RNA aliquots provided by the Biorepository with the goal of correlating finding to treatment response.

2.6.4 **Imaging correlates**

Brain MRI scans will be performed to assess treatment response. MRI may also be performed to better understand the biological impact that the experimental treatment is having on the tumor. In addition to routine MRI sequences (T1, T2), we will perform perfusion, and diffusion tensor imaging to non-invasively and serially measure structural and functional changes in the tumor vasculature and tumor microenvironment. The advanced MRI techniques described above have successfully been incorporated into prior GBM clinical trials using cediranib and revealed useful insights into cediranib's mechanisms of action.

Of particular relevance to this study, these MRI techniques have successfully measured changes in tumor vasculature and perfusion so will shed light on the role hypoxia is hypothesized to play in promoting the synergistic effect of PARP inhibition and VEGF inhibition. Incorporation of the techniques to this trial should allow us to further optimize the development of these combinations of drugs (Batchelor 2013).

Patients will undergo advanced MRI scans prior to initiation of treatment (baseline), prior to cycle 3 day 1 and then every 2 months thereafter during treatment. These physiological MRI studies will only be pursued if there is sufficient capability among sites to perform these studies. We hope to accure at least 20 patients for advanced MRI correlative study.

3. PATIENT SELECTION

3.1 Eligibility Criteria

1. Unequivocal evidence of progressive disease on contrast-enhanced brain CT or MRI as defined by RANO Criteria, or have documented recurrent glioblastoma on diagnostic biopsy.

2. Previous therapy with at least radiotherapy and temozolomide.

3. Must be 12 weeks from radiotherapy. If patients are within 12 weeks of radiotherapy, then the progressive lesion must be outside of the high-dose

radiation target volume or have unequivocal evidence of progressive tumor on a biopsy specimen.

4. Only first and second recurrences of GBM are eligible

5. From the projected start of scheduled study treatment, the following time periods must have elapsed: 5 half-lives from investigational agents, 4 weeks from cytotoxic therapy (except 23 days for temozolomide and 6 weeks from nitrosoureas), 6 weeks from antibodies, or 4 weeks (or 5 half-lives, whichever is shorter) from other systemic anti-tumor therapies. Treatment on study may start one day after discontinuation of the optune device.

6. All adverse events Grade > 1 related to prior therapies (chemotherapy, radiotherapy, and/or surgery) must be resolved, except for alopecia.

7. Willingness to release archival tissue sample for research purposes, if available.

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

9. Karnofsky performance status ≥ 60 (see Appendix A)

10. Life expectancy of at least 3 months

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

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- Hemoglobin ≥ 10.0 g/dL and no blood transfusions in the 28 days prior to entry/randomization
- total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- Creatinine should not exceed the institutional upper limit of normal
  OR creatinine clearance ≥60 mL/min/1.73 m^2

12. Urine protein:creatinine (UPC) ratio < 1 or urine dipstick for proteinuria ≤ 2+ (note: if the UPC ratio is ≥ 1 then a 24-hour urine collection should be performed and this must demonstrate ≤ 1g of protein in 24 hours)

13. CT or MRI within 14 days prior to start of study drug.

14. Corticosteroid dose must be stable or decreasing for at least 5 days prior to the baseline MRI scan.

15. The effects of olaparib and cediranib on the developing human fetus are unknown. Female subjects must either be of non-reproductive potential, not breast-feeding or must have a negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on day 1. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of olaparib + cediranib administration.

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

3.2 Exclusion Criteria

1. Participants should not have received any other investigational agents nor have participated in an investigational drug trial within the past 4 weeks.

2. Participants may not have had prior use of PARP inhibitors. Patients may not have received prior treatment affecting the VEGF pathway including but not limited to thalidomide, bevacizumab, sunitinib, or sorafenib.

3. Patients who are receiving any other investigational agents.

4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib, cediranib or bevicizumab.

5. Participants may not have any evidence of ongoing inadequately controlled hypertension (defined as a systolic BP of >140 mmHg or a diastolic BP of >90 mmHg). Patients with hypertension may not be on more than three antihypertensive medications for management of their blood pressure (medications that combine two anti-hypertensives into one are considered as two medications). It is strongly recommended that patients who require three antihypertensive medications for baseline management of pre-existing hypertension be actively followed by a cardiologist or blood pressure specialist for management of BP while on protocol.

6. Participants may not have had any prior history of hypertensive crisis or

hypertensive encephalopathy.

7. Participants may not have had history of abdominal fistula or gastrointestinal perforation within the past 6 months.

8. Participants may not have had a history of intra-abdominal abscess within the past 6 months.

9. Patients may not have a known or confirmed history of pneumonitis.

10. Participants may not have current signs and/or symptoms of bowel obstruction or signs and/or symptoms of bowel obstruction within 3 months prior to starting study drugs

11. Participants may not have a dependency on IV hydration or TPN.

12. Patients with myelodysplastic syndrome/acute myeloid leukemia

13. Participants with any concomitant or prior invasive malignancies are ineligible with the following exceptions:
    - Treated limited-stage basal cell or squamous cell carcinoma of the skin
    - Carcinoma in situ of the breast or cervix
    - Prior cancer treated with curative intent with no evidence of recurrent disease 3 years following diagnosis and judged by the investigator to be at low risk of recurrence.

14. Participants with any of the following:
    - History of myocardial infarction within six months
    - Unstable angina
    - History of CVA within 6 months
    - New York heart association grade II or greater congestive heart failure
    - Significant vascular disease (e.g. aortic aneurysm, history of aortic dissection)
    - Clinically significant peripheral vascular disease

15. If cardiac function assessment is clinically indicated or performed: participants will be ineligible if left ventricular ejection fraction (LVEF) is less than normal per institutional guidelines, or <55%, if the threshold for normal is not otherwise specified by institutional guidelines.

16. Participants may not have QTc >470msec or family history of long QT syndrome.

17. Participants may not have a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to starting cediranib. Anticipation of need for major surgical procedures during the course of the study also excludes patients

from the trial.

18. Participants should not have any 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.

19. Participants receiving any medications or substances that are *strong* inhibitors or inducers of CYP3A4 or *moderate* inhibitors of CYP3A4 are ineligible (see Appendix B). The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. 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. Dihydropyridine calcium-channel blockers are permitted for management of hypertension. Appendix C (Patient Drug Information Handout and Wallet Card) should be provided to patients.

20. Pregnant women are excluded from this study because *cediranib and olaparib* agent 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 *cediranib and olaparib* breastfeeding should be discontinued if the mother is treated with *cediranib and olaparib.* These potential risks may also apply to other agents used in this study

21. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with *cediranib and olaparib.* 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.

22. Current use of a prohibited medication. The following medications or non-drug therapies are prohibited:
    - Other anti-cancer therapy while on study treatment
    - Concurrent treatment with bisphosphonates is permitted; however, treatment must be initiated prior to the first dose of study therapy. Prophylactic use of bisphosphonates in patients without bone disease is not permitted, except for the treatment of osteoporosis.
    - Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is prohibited during the study (including, but not limited to, cannabis, S. John's wort, kava, ephedra [ma huang], gingko biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto or ginseng).
    - Raloxifene is allowed for patients taking it for bone health.

23. Participants should not have evidence of coagulopathy or bleeding diathesis. Therapeutic anticoagulation for prior thromboembolic events is permitted.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

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

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	

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

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

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

For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm.

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 the following:

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

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

- Active registration status

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

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

4.2.1 **Downloading Regulatory Documents**

Site registration forms may be downloaded from the *10067* 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 to expand, and then select LAO-MA036 and protocol #10067."
- 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 *NCI protocol* 10067 Site Registration:**

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- ETCTN Specimen Tracking Training – please refer to the memo dated 10/03/2017 posted on the CTSU website for further details
- SIV Attestation for new participating sites
- Pharmacy Training Attestation for new participating sites
- Protocol Signature Page and Training Attestation

For protocol amendents, the following will be required:

- 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)
- Protocol Signature Page and Training Attestation
- Pharmacy Training Attestation if the amendment significantly impacts study drug ordering, handling, storage or accountability.

4.2.3 **Submitting Regulatory Documents**

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

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

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

4.2.4 **Checking Site Registration Status**

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

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

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

4.3 Patient Registration

4.3.1 **OPEN / IWRS**

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

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: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- 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 **Special Instructions for Patient Enrollment**

For the ETCTN Biobanking and Molecular Characterization Initiative, the following information will be requested:

- Protocol Number
- Investigator Identification
    - Institution and affiliate name
    - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
    - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a

Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the ETCTN Biobanking and Molecular Characterization portion of this protocol. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID) and the IWRS-assigned UPID for this trial. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.**

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 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.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 14 days 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. The cycle length is 28 days, and patients will undergo cancer assessment per RANO criteria after every 2 cycles of therapy.
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.

5.1.1 **Arm 1 (investigational)**

Agent	Dosing Instructions	Dose	Route	Schedule	Cycle Length
Olaparib	Orally BID at the same times each day	200 mg	PO	Twice daily and continuously	28 days (4 weeks)
Cediranib	Orally each morning on an empty stomach, either 1 hour before or 2 hours after breakfast	30 mg	PO	Daily and continuously	28 days (4 weeks)

Patients will be required to maintain an accurate medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle.

5.1.2 **Arm 2 (Reference)**

Agent	Dosing Instructions	Dose	Route	Schedule	Cycle Length
Bevacizumab	Intravenously every two weeks (± 3 days) per institutional guidelines with associated pre-medications.	10mg/kg	IV	Day 1 and 15 of 28 day cycles	28 days (4 weeks)

Patient's weight will be checked prior to each dose of bevacizumab. Dose will be adjusted if there is a >5% change in weight.

5.1.3 **Pre-treatment Criteria**

5.1.3.1 Screening

Patients must meet criteria at screening as outlined in Section 3.1 Inclusion Criteria and 3.2 Exclusion Criteria.

5.1.3.2 Hematologic parameters

Patients must meet the following absolute neutrophil count (ANC) and hematologic parameters for treatment.

For Arm 1 (olaparib and cediranib)

For C1D1: ANC ≥ 1500 cells/μL, Platelets ≥ 100,000 cells/μL, Hemoglobin ≥ 9 g/dL
For subsequent cycles: ANC ≥ 1000 cells/μL, Platelets ≥ 100,000 cells/μL, Hemoglobin ≥ 9 g/dL

For Arm 2 (bevacizumab)
For C1D1 should be: ANC ≥ 1500 cells/μL, Platelets ≥ 100,000 cells/μL, Hemoglobin ≥ 9 g/dL
For C1D15 and subsequent cycles (including Day 15), platelets must be ≥ 75K and ANC ≥ 1000 cells/μL

5.1.4 **Treatment Administration**

5.1.4.1 Cediranib

Cediranib at the appropriate dose level will be given orally continuously each morning on an empty stomach, either 1 hour before or 2 hours after breakfast. Subjects have up to to 2 hours to make up any missed dose. Subjects should not however "make up" a dose that was vomited. Subjects should take cediranib with a glass of water. The cediranib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

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

Frequent blood pressure monitoring is important in patients receiving cediranib. Clinical trials of cediranib demonstrate that increases in blood pressure may occur following dosing with cediranib for a number of weeks and that these increases may occur relatively quickly when starting the drug. Patients will be asked to record twice-daily blood pressure readings (Appendix E). If two successive systolic readings are >140 mmHg OR two successive diastolic readings are >90 mmHg OR any combination of elevated systolic and diastolic blood pressure are observed, patients will be instructed to contact their physician as soon as possible. Patients should seek medical advice if their BP exceeds 180 mmHg (systolic) or 105 mmHg (diastolic) at any time and should also be encouraged to contact their physician if they are concerned about any symptoms that may be associated with high blood pressure (*e.g.*, headache). Section 7 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension. Blood pressure cuffs will be provided to patients for blood pressure monitoring.

5.1.4.2 Olaparib

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

approximately 240 mL of water. The morning dose may be taken approximately 1 hour after the cediranib dose, following a light meal/snack. The evening dose may be taken with a light meal/snack. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

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

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

5.1.4.3 Bevacizumab

Bevacizumab should be administered as a intravenous infusion using a rate–regulating device per institutional guidelines with associated pre-medications. Do not administer as an IV push or bolus. Anaphylaxis precautions should be observed during administration.

If no institutional guidelines exist, follow below:

> Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer subsequent doses over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

If a patient experiences an infusion-associated adverse reaction, he or she will be monitored according to institutional guidelines and may be pre-medicated for the next study drug infusion.

5.1.4.4 MRI Scan

MR scans will be performed with the same sequences at baseline and after every two cycles of treatment. Sequences will include T1- and T2-weighted volumetric images, fluid attenuated inversion recovery (FLAIR), DWI/diffusion tensor imaging (DTI), and T2/T2*-weighted perfusion scans (Dynamic contrast susceptibility MRI) where available. The "Autoalign" package or similar available from the manufacturer will be used to achieve the same slice prescription in the same patient at each visit. Each MRI will last ~45 minutes vs. ~30-40 minutes for standard brain MRIs.

Please refer to Appendix F for details on the imaging protocols.

5.2 General Concomitant Medication and Supportive Care Guidelines

Cediranib demonstrated minimal inhibitory effects on the activity of CYP3A4 (testosterone and midazolam) *in vitro*, although the IC50 was far in excess of the clinically relevant concentrations. Based on *in vitro* and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. However, *in vitro* data have also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4. Given these data, potent inhibitors or inducers of CYP3A4 as outlined in Appendix B must not be used during this study for patients receiving olaparib. Moderate inhibitors of CYP3A4 should be avoided. If the inhibitor cannot be avoided, the olaparib tablet should be reduced by 50% during the duration that the patient remains on the moderate CYP3A4 inhibitor, as per below the table below. Dihydropyridine calcium-channel blockers are allowed for management of hypertension.

Olaparib tablet dose	**Olaparib tablet dose on moderate CYP3A inhibitor**
200mg BID	100mg BID
150mg BID	150mg daily (patient should take AM dose)
100mg BID	100mg daily (patient should take AM dose)

Because of the potential for interaction of olaparib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Subjects should avoid grapefruit juice while on study, due to P450 interactions

Patient should receive general concomitant and supportive care medications based on best medical practice. Neupogen and other bone marrow-supportive agents, including erythropoiesis stimulating agents, are not allowed during treatment.

Caution should be taken with concomitant use of any medication that may markedly affect renal function. Such medications may be used with caution if deemed essential for treatment or may be continued if already in use prior to entry in the study with no effect on renal function

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

Frequent **blood pressure monitoring** is important in patients receiving cediranib. Experience to date suggests that increases in blood pressure may occur following dosing with cediranib for a number of weeks and that these increases may occur over a relatively short time frame. It is imperative that the investigator institute appropriate measures to control BP. This may necessitate changes to existing antihypertensive medication, addition of new medication(s), and/or interruption/withdrawal of cediranib. Patients will be provided blood pressure cuffs and instructed how to use them by each clinical site. Patients must be able and willing to monitor their blood pressure on a twice daily basis. Section 7 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension.

Because of the rapid changes in blood pressure that can occur and the potential for severe life threatening complications if hypertension is not appropriately managed, patients should check their blood pressure twice daily for at least the first 8 weeks after starting study drug, or, if antihypertensive management is required, until a stable anti-hypertensive regimen has been established, even if this requires more than 8 weeks. After 8 weeks or once a stable regimen has been achieved, blood pressure monitoring may be reduced to once daily. Twice daily monitoring should be re-implemented after any cediranib hold/dosing delay for two weeks or until the patient is re-established on a stable anti-hypertensive regimen, whichever takes longer. Patient blood pressures should be reviewed with the study team on a weekly basis for the first 8 weeks of study treatment to ensure that blood pressure guidelines are being correctly followed.

Cediranib can impair healing. For this reason, cediranib should be held two weeks prior to any surgical procedures and may be restarted when the surgical wound is healed. Patients who have had major surgical procedure, open biopsy, or significant traumatic injury within 28 days of starting cediranib are not eligible for the study, as per Section 3.2.

5.3 Duration of Therapy

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

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

5.4 Duration of Follow Up

Patients will be followed *for 30 days after* removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. All participants' vital status may befollowed after removal from the study treatment using publically available databases. All patients who are removed from study treatment, regardless of rationale, will be followed for survival once off study for 3 years. Subjects will be followed for survival every 30 days after coming off study.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications until March 31, 2018. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. A copy of the CTCAE version 5.0 can be downloaded from the CTEP websitehttp://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Parameters for All Cycles

Patients must meet the following parameters to proceed with treatment. Patients who do not meet these criteria may resume treatment later in the cycle once criteria are met. Cycles and days are numbered continuously regardless of any dose holds or delays in resumption of treatment. Study drugs may be help for up to 28 days.

For Arm 1 (olaparib and cediranib)
For C1D1

- ANC ≥ 1500 cells/µL
- Platelets ≥ 100,000 cells/µl
- Hemoglobin ≥ 9 g/dL
- Creatinine ≤ 2.0 x ULN unless UPC is > 1.0 or urine dipstick is > 2+. Refer to section 6.2.5 if UPC is > 1.0 or urine dipstick is > 2+.
- Adequate blood pressure control, as detailed in Section 6.2.3.
- Liver function tests (AST and ALT) ≤ 2.5 x the institutional upper limit of normal; note: patients can hold study treatment up to 28 days until liver function tests are within parameters to proceed with treatment. For grades ≥ 2 AST and/or ALT elevations, please follow instructions in Section 6.2.2 (General Management of Adverse Events).
- Urine protein:creatinine ratio OR urine dipstick protein as detailed in Section 6.2.5

For C1D15 and subsequent cycles (including all Day 15): Same as above *except* ANC ≥ 1000 cells/µL

For Arm 2 (bevacizumab)
For C1D1:

- ANC ≥ 1500 cells/µL
- Platelets ≥ 100,000 cells/µL

- Hemoglobin ≥ 9 g/dL
- Creatinine ≤ 2.0 x ULN
- Adequate blood pressure control, as detailed in Section 6.3.1.
- Proteniuria: ≤ 2+ proteinuria as detailed in Section 6.3.1.

For C1D15 and subsequent cycles (including all Day 15): same as above *except* platelets can be ≥ 75,000 and ANC ≥ 1000 cells/μL

6.2 Olaparib and Cediranib

6.2.1 Olaparib and Cediranib Dose Modification Tables

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

Dose Level	Olaparib tablets
-2	100 mg twice daily
-1	150 mg twice daily
1	200 mg twice daily

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

6.2.2 General Management of Adverse Events

The management of general adverse events not otherwise specified will be as per the table below. Management of specific toxicities, including hypertension, proteinuria, decreased in LVEF, diarrhea, fever and neutropenia, nausea and vomiting, thyroid toxicities, reversible posterior leukoencephalopathy syndrome (RPLS), and gastrointestinal perforation will be as further outlined in specific sections 6.2.3-6.2.13

Table 6.2.2A: General Management of Adverse Events (Non-hematologic) for cediranib / olaparib	
Observation	**Action**
AE resolves promptly with supportive care	Maintain dose level
Any grade 2 non-hematologic AE or for creatinine ≥ 2 x ULN (excluding hypertension or other AEs with specific management instructions outlined in the sections below, or easily correctable asymptomatic grade 2 laboratory abnormalities) related to study drug(s) that persists despite maximal support.	Hold study drug(s)[1] for up to 14 days until toxicity resolves to ≤ grade 1 or: a) for AST/ALT until it resolves ≤ 2.5 ULN or b) for creatinine until it resolves < 2 x ULN[1]. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 7.1, at the treating investigator's discretion.[2] The overall PI of the study should be informed regarding all dose modifications. Patients whose toxicity has not resolved after 14 days will be removed from study. Patients experiencing persistent Grade 2 fatigue that is felt to be acceptable by both patient and treating investigator may continue on study drug without dose hold or reduction at the treating investigator's discretion.
Any ≥ grade 3 non-hematologic (excluding grade 3 hypertension or easily correctable symptomatic grade 3 laboratory abnormalities)	Hold study drug(s)[2] for up to 14 days until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 7.1, at the treating investigator's discretion.[3] The study PI of the study should be informed regarding all dose modifications.
1. Grade 3 or 4 non-hematologic AE related to cediranib and olaparib combination that does not resolve to grade 0-2 within 14 days despite maximum supportive care after treating patient at the lowest reduced dose level.[4] **2.** Grade 3 or 4 non-hematologic AE related to cediranib/olaparib lasting >14 days despite maximum supportive care and treatment being held.	Remove patient from study.

1. Note: creatinine threshholds are different in the prescense of concurrent proteinuria. Please refer to section 6.2.5 if urine dipstick is greater than 2+ or UPC > 1.0.
2. At the discretion of the investigator, the study drugs may be held or dose modified independently if the observed toxicity is attributed to only one of the drugs, while the patient continued to receive the drug not associated with the observed toxicity. The time a given drug is held should not exceed 14 days.

3. Patients who are at the lowest reduced dose level may have their drug resumed at that dose level after discussion with the overall PI.
4. Excluding hypertension. For thromboembolic events, treatment may be resumed at the discretion of the investigator once patient is asymptomatic.

Table 6.2.2B: General Management of Adverse Events (Hematologic) for cediranib / olaparib

Observation	Action
Absolute neutrophil count ≥ 1000/μL **AND** Platelets ≥ 100,000/μL **AND** Hemoglobin ≥ 9 g/dL	Maintain dose level
Absolute neutrophil count < 1000/μL **OR** Platelets < 100,000/μL **OR** Hemoglobin < 9 g/dL	Hold treatment for up to 14 days until absolute neutrophil count ≥1000/μL, platelets >100,000/μL, and hemoglobin ≥9 g/dL. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as perthe dose reduction levels in Section 7.1, at the treating investigator's discretion. The study PI of the study should be informed regarding all dose modifications. Patients whose counts have not recovered to absolute neutrophil count ≥1000/μL, platelets ≥100,000/μL, and hemoglobin ≥9 g/dL after 14 days should be removed from study.
Grade 4 hematologic AE related to cediranib or olaparib that does not resolve to absolute neutrophil count ≥1000/μL, platelets ≥100,000/μL, and hemoglobin ≥9 g/dL despite maximum supportive care after 14 days.	Remove patient from study.

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

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

6.2.3 **Hypertension**

Increases in BP and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following cediranib treatment has been seen in animal studies as well as clinical trials.
Only doses of cediranib will be modified for hypertension; olaparib doses will not be reduced unless other toxicities are experienced. Patients receiving cediranib will be provided with blood pressure monitors for home use and will check and record their blood pressures at least twice daily while on study treatment.

See the table below for guidelines on hypertension management and Appendix G for suggested antihypertensive medications by class.

Note:

- If patients require a delay of >2 weeks for management of hypertension, management should be discussed with the overall PI and may require discontinuation from protocol therapy
- Patients may have up to 4 drugs for management of hypertension prior to any dose reduction in cediranib.
- Hypertension should be graded using the NCI CTCAE. Patients with baseline hypertension who require the addition of new medications for hypertension management while on study drug may not have an increase in CTCAE grade, but a change in attribution should be noted.
- 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.

Table 6.2.3: Hypertension Monitoring and Management
• See Appendix G for suggested antihypertensive medications by class • Abbreviations: Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARB), selective beta blockers (BB), Dihydropyridine calcium channel blockers (DHP-CCP) • If patients require a delay of >2 weeks for management of hypertension, discontinuation of cediranib or protocol therapy may be considered after discussion with the Study PI. • Patients may have up to 4 drugs for management of hypertension prior to any dose reduction in cediranib • Hypertension should be graded using the NCI CTCAE. Please note: patients may have baseline hypertension meeting CTCAE grading criteria on study entry. Should patients require increase in dosing of BP medication or increased number of medications, they should then be noted to have hypertension related to study drug, with grading as per CTCAE criteria. Baseline grade of hypertension should also be recorded in the patient's record.

• Note: Stopping or reduce the dose of cediranib is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly.				
Toxicity Severity	**Definition**	**Antihypertensive Therapy**	**Blood Pressure Monitoring**	**Cediranib Dose Modification**
Grade 1	Asymptomatic transient (<24 hours) increase by >20 mmHg diastolic or to > 140/90 mmHg if previously within normal limit	Consider early initiation of BP medication for BP > 140/90 mmHg that is confirmed on a second reading. Cediranib can cause rapid escalation in BP, and early initiation of BP management can reduce likelihood of HTN-related complications.	Continue standard BP monitoring per treating doctor and confirm resolution of BP to <140/90 mmHg within 24 hours	None
Grade 2	Recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limit. Monotherapy may be indicated	Initiate BP medication for first line treatment. *Suggestions:* ACE-inhibitor. Escalate dose of medication in stepwise fashion until BP is controlled or at a maximum dose. If BP is not controlled to < 140/90 mmHg with one drug regimen, then add a second agent. **Study drug does not need to be held unless otherwise clinically necessary.**	Increase frequency of monitoring until stabilized to BP <140/90 mmHg.	Do not hold cediranib unless otherwise clinically necessary.

		Consider renal consult.		
Grade 3	Requiring more than one drug or more intensive therapy than previously.	Maximize 2 drug Regimen. • *Suggestions:* ACE-inhibitor +BB Escalate doses of existing medication until BP is controlled or at a maximum dose. If BP is not controlled to < 140/90 mmHg with two drug regimen, then add a third agent. **Study Drug will not be held during trial of two drug combinations. Additional antihypertensive drugs, up to a total of 4, may be maximized for blood pressure control.** *Consider consult with a blood pressure management specialist if more than 3 drugs are required for BP control.*	Increase frequency of monitoring until stabilized to BP <140/90 mmHg.	Do not hold cediranib or other study drugs unless BP is not decreased to < 150/100 mmHg 48 hours after multi-drug therapy is instituted or if clinical symptoms worsen (e.g. headache). If BP is not controlled to less than 150/100 mmHg with maximal therapy or if clinical symptoms worsen, then withhold cediranib (up to 3 weeks) until maximum effect of the antihypertensive agents is achieved. If BP is reduced to Grade 1 within 3 weeks, cediranib may be resumed at prior dose.
Grade 4	If threatening consequences	Initiate treatment	Intensive BP monitoring	**Hold cediranib.**

	OR SBP ≥ 180mmHg OR DBP ≥ 110mmHg	Hospitalize patient for ICU management, IV therapy as necessary. 14 days are allowed to maximize the full effect of anti-hypertensive agents.	(hospitalization if necessary)	If BP is reduced to <140/90mmHg within 14 days, cediranib may be resumed at a reduced dose after discussion with the Study PI and/or sponsor.

6.2.4 **Diarrhea**

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

Table 6.2.4: Management of Diarrhea	
Toxicity Severity	**Management / Modifications**
Initial grade 1 or 2	Patients can take loperamide (per standard practice) and continue to take loperamide until patients are free from diarrhea for at least 12 hours. The dose of loperamide should not exceed 16 mg in a 24-hour period.
	If diarrhea persists despite 24 hours of loperamide treatment, hold cediranib for a maximum of 7 days, continue loperamide, and maintain hydration. Cediranib may be restarted at the same dose once patients have been free from diarrhea for 12 hours.
Persistent grade 2 or grade 3 or 4	Follow section 7.2

6.2.5 **Proteinuria**

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

Table 6.2.5: Management of Proteinuria		
Proteinuria Value if following by U/A	**Monitoring**	**Dose modification**

> 2+ on urine dipstick or U/A AND Creatinine ≤ 1.5 x ULN	Perform UPC	Continue study drugs at planned dose.
> 2+ on urine dipstick or U/A AND Creatinine > 1.5 x ULN	Perform UPC	**Hold cediranib** until results of UPC are known and see below.
Based on results of the UPC[1]:		
UPC ≤ 1.0 AND Creatinine ≤ 2 x ULN	Continue monitoring prior to each cycle as per previous.	Continue study drugs at planned dose.
UPC > 1.0 and ≤ 3.5 AND Creatinine ≤ 1.5 x ULN	Perform UPC prior to each cycle.	Continue study drugs at planned dose.
UPC > 3.5 OR UPC > 1.0 AND Creatinine > 1.5 x 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 x ULN, resume cediranib with reduction in cediranib by one dose level. Consider consultation with nephrologist.
[1]If creatinine is > 2x ULN regardless of UPC or urine dipstick then hold cediranib for up to 14 days. Refer to section 6.2.2.		

6.2.6 **Decrease in LVEF**

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

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

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

Table 6.2.6: Management and Monitoring of Decreased LVEF			
Relationship of LVEF to Institution's LLN	**LVEF Decrease <10%**	**LVEF Decrease 10-15%**	**LVEF Decrease ≥ 16%**
Normal	Continue	Continue	Continue and repeat MUGA/ECHO within 1-2 cycles. If LVEF decrease persists, remove from protocol therapy.

Patients with symptomatic decrease in LVEF attributable to study drugs should be removed from protocol therapy.

6.2.7 **Fever and Neutropenia**

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

6.2.8 **Nausea and Vomiting**

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

6.2.9 **Thyroid Toxicities**

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

Table 6.2.9: Management and Monitoring of Thyroid Toxicities	
Results of TSH, T4, and T3	**Action**
Increases in TSH with normal T4/T3	Monitor
Increase in TSH with normal T4/T3 and adverse events suggestive of incipient hypothyroidism	Consider replacement thyroxine
Increase in TSH with reductions in T4 and T3	Consider replacement thyroxine

In all of the above cases, study treatment should continue unless clinically contraindicated.

Referral to an endocrinologist should also be considered if thyroid abnormalities occur. Patients already on thyroid replacement hormone who require adjustment of their replacement regimen will be considered to have a drug-related toxicity.

6.2.10 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

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

6.2.11 Gastrointestinal Perforation

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

6.2.12 Rotator Cuff Injury

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

Table 6.2.12: Management of Rotator Cuff Symtoms

Severity	Symptoms / Findings	Action	Dose modification
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Limit heavy lifting or carrying of heavy objects, bags or backpacks. Consider shoulder MRI if symptoms warrant.	None
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Obtain shoulder MRI if not previously obtained. If rotator cuff injury present on MRI, refer for physical therapy.	Hold cediranib and olaparib for up to 14 days until symptoms resolve to Grade 1 or less. Cediranib and olaparib may then be resumed at a reduced

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

6.2.13 **Myelodysplatic Syndrome**

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.

6.3 Bevacizumab

6.3.1 **Bevacizumab Dose Modifications**

Note 1: There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below
Note 2: <u>If bevacizumab is interrupted for ANY reasons for >4 weeks (unless otherwise specified),</u> the patient should discontinue bevacizumab therapy on protocol.

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE Grade**	**Action to be Taken**
Allergic reactions Or **Infusion-related reactions** Or **Anaphylaxis**	Grade 1-2	• Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. • For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. • Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Arterial), arterial ischemia - Cardiac ischemia - Myocardial infraction - CNS ischemia (TIA, CVA) - Any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (new or worsening since bevacizumab	Discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Venous)	[Note: Patients with primary lung cancer requiring therapeutic anticoagulation should discontinue bevacizumab]	
	Grade 3 OR asymptomatic Grade 4	▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ▪ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation **IF** <u>all</u> of the criteria below are met: - The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE Grade**	**Action to be Taken**
		involving major vessels or other conditions) - The subject must not have had hemorrhagic events while on study - The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab
Hypertension	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1 (SBP 120-139 mmHg or DBP 80-89 mmHg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mmHg)	Begin anti-hypertensive therapy and continue bevacizumab
	• Grade 2 symptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg) • Grade 3 (SBP $\geq$160 mmHg or DBP $\geq$100 mmHg)	• Start or adjust anti-hypertensive medication • Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg* • For hypertension that is refractory requiring delay of bevacizumab for > 4 weeks, discontinue bevacizumab
	Grade 4 (Hypertensive crisis or malignant hypertension)	Discontinue bevacizumab

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE Grade**	**Action to be Taken**
Heart Failure OR **Left Ventricular (LV) dysfunction**	• Heart failure ≥Grade 2 • LV dysfunction ≥Grade 3	Discontinue bevacizumab
Proteinuria Proteinuria will be monitored by urine analysis dipstick. If Dipstick ≥2+ proteinuria, 24-hour urine protein should be obtained	Dipstick ≥ 2+	Hold bevacizumab and obtain 24 hour urine protein
	If 24-h urine protein <2g	Continue bevacizumab
	If 24-h urine protein ≥2 g	• Hold bevacizumab until 24-hour urine protein <2.0 g • Discontinue bevacizumab if urine protein does not recover to < 2.0 g after 8 weeks of bevacizumab interruption
	Nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (intracranial or pulmonary)	Grade 2-4	• Discontinue bevacizumab
	Grade 1	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and hemoglobin is stable - there is no bleeding diathesis that would increase the risk of therapy • there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence
Hemorrhage (not CNS or pulmonary)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and hemoglobin is stable

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE Grade**	**Action to be Taken**
		- there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome OR **PRES** (Posterior Reversible Encephalopathy Syndrome)	Any Grade	Discontinue bevacizumab upon diagnosis of RPLS.
Wound dehiscence OR **Wound complications**	Grade 2	Hold bevacizumab until healing
	Grade 3-4	Discontinue bevacizumab
Perforation (GI, or any other organ)	Any Grade	Discontinue bevacizumab
Fistula (GI, pulmonary or any other organ)	Any Grade	Discontinue bevacizumab
Obstruction of GI tract	Grade 2 requiring medical intervention	Hold bevacizumab until complete resolution
	Grade 3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after 28 days and full recovery from surgery, and at investigator's discretion
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	• Hold bevacizumab until symptoms resolve to≤Grade 1
	Grade 4	• Discontinue bevacizumab • **Upon consultation with the study chair,** resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the Grade 4 toxicity is transient, has recovered to ≤Grade 1 and unlikely to recur with retreatment.

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 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

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

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

7.1.1 CAEPRs for CTEP IND Agents

7.1.1.1 CAEPR for Olaparib

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

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

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

Version 2.4, 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 4)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
	Creatinine increased		
	Lymphocyte count decreased		
	Neutrophil count decreased		
	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; Muscle weakness lower limb; Myalgia; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (decreased glomerular filtration rate); Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Pruritus; Rash maculo-papular
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: Olaparib (AZD2281) in combination with other agents could cause an exacerbation of any adverse

event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for Cediranib

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Cediranib (AZD2171, NSC 732208)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1608 patients.* Below is the CAEPR for Cediranib (AZD2171).

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

Version 2.15, November 7, 2018[1]

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
ENDOCRINE DISORDERS			
	Hyperthyroidism		
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis		***Anal mucositis (Gr 2)***
	Constipation		***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dysphagia		***Dysphagia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal perforation[3]	

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

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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (polycythemia); Bone marrow hypocellular; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (premature ventricular complexes); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Mobitz (type) II atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ears feel full/plugged); Ear

and labyrinth disorders - Other (viral labyrinthitis); Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (blindness); Eye disorders - Other (visual disturbance); Papilledema; Photophobia; Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Bloating; Colitis; Colonic obstruction; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Flatulence; Gastric necrosis; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (hydrops); Gastrointestinal disorders - Other (tongue sensitivity); Ileus; Oral pain; Periodontal disease; Peritoneal necrosis; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Fever; Gait disturbance; Hypothermia; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder obstruction; Hepatic pain; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice cholestatic)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture; Injury, poisoning and procedural complications - Other (tracheostomy malfunction); Intestinal stoma leak; Venous injury; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Hemoglobin increased; INR increased; Investigations - Other (elevated ammonia level); Investigations - Other (increased blood erythropoietin); Lipase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Avascular necrosis; Back pain; Bone pain; Chest wall pain; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Myalgia; Myositis; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Central nervous system necrosis; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Encephalopathy; Hydrocephalus; Ischemia cerebrovascular; Memory impairment; Muscle weakness left-sided; Nervous system disorders - Other (coma); Nervous system disorders - Other (right hemiparesis); Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Spinal cord compression; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Confusion; Delirium; Depression; Hallucinations; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Cystitis noninfective; Hematuria; Urinary retention; Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Menorrhagia; Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fistula; Pulmonary hypertension; Sinus pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pruritus; Purpura; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (petechiae); Skin and subcutaneous tissue disorders - Other (plantar warts); Skin ulceration; Urticaria
VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hypotension; Vasculitis

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

7.1.1.3 CAEPR for Bevacizumab

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMAb VEGF, NSC 704865)

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 3540 patients.* Below is the CAEPR for Bevacizumab (rhuMAb VEGF).

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

Version 2.5, May 2, 2018[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
		Hemolytic uremic syndrome	
CARDIAC DISORDERS			
	Cardiac disorders - Other (supraventricular arrhythmias)[2]		***Cardiac disorders - Other (supraventricular arrhythmias)[2] (Gr 3)***
		Chest pain - cardiac[3]	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction[3]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***
	Gastrointestinal obstruction[6]		
		Gastrointestinal perforation[7]	
		Gastrointestinal ulcer[8]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
HEPATOBILIARY DISORDERS			
		Gallbladder perforation	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fascitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		***Infusion related reaction (Gr 2)***
		Injury, poisoning and procedural complications - Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dehydration		***Dehydration (Gr 3)***
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
		Avascular necrosis[11]	
	Generalized muscle weakness		
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[12]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[13]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy[14]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr 3)***
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[15]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***
	Hoarseness		***Hoarseness (Gr 3)***
		Pulmonary hypertension	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism[3,16]	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***

[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]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation, and atrial flutter.

[3]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

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

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.

[11]There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.

[12]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[13]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[14]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[15]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[16]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye pain; Floaters; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Vitreous hemorrhage; Watering eyes
GASTROINTESTINAL DISORDERS - Ascites; Cheilitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Osteonecrosis; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Myasthenia gravis; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Dysuria; Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Nail loss; Pain of skin; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

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

7.2 Adverse Event Characteristics

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

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

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

7.3 Expedited Adverse Event Reporting

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

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

7.3.2 Distribution of Adverse Event Reports

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

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports. Expedited reporting is required for any serious adverse event (SAE) that occurs after the initial dose of treatment, during treatment or within 30 days of the last administration of treatment in accordance with below.

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

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

Late Phase 2 and Phase 3 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 **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** 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 **<u>ANY</u>** 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).

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

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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

<u>Expedited AE reporting timelines are defined as:</u>

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

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

Expedited 10 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

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

7.5 Secondary Malignancy

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

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

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

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

7.6 Second Malignancy

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

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 8.1.

8.1 CTEP IND Agent(s)

8.1.1 Olaparib (AZD2281) (NSC 747856)

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

Other Names: AZD2281; KU-0059436; CO-CE 42
Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

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

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

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

Description: crystalline solid

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

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

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

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

Storage: Store in a secure location below 30° C (86° F). Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the

opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.

Stability: Shelf-life studies are ongoing.
If a storage temperature excursion is identified, promptly return olaparib (AZD2281) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Route and Method of Administration: Tablets are taken by mouth and can be taken with a light meal/snack if needed to reduce stomach irritation.

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. It is not known whether olaparib is found in seminal fluid, so as a precaution, male study participants must use a condom during treatment and for three (3) months after the last dose and should avoid fathering a child or donating sperm during this same time period. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

Lactation is a protocol exclusion criterion and not advised since there is potential for serious adverse reactions in breastfed infants. Advise lactating women to not breastfeed during study treatment and for one (1) month after receiving the last dose of olaparib.

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.

There are no data on the effect of olaparib on wound healing, therefore as a precaution, olaparib treatment should be stopped at least 3 days prior to planned surgery. After surgery olaparib can be restarted when the wound has healed. No stoppage of olaparib is required for any needle biopsy procedure.

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

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

Olaparib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 **Cediranib (AZD2171) (NSC 732208)**

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

Other Names: Cediranib, AZD2171 maleate, Recentin™

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

Molecular Formula: C25H27FN4O3 · C4H4O4

Molecular Weight: 566.59 as maleate salt (450.52 as free base)
Approximate Solubility: The aqueous solubility of AZD2171 is 0.0006 mg/mL for the free base (distilled water, pH 8.1 at 25°C) and 1.9 mg/mL for the maleate salt (distilled water, pH 4.4 at 25°C).

Mode of Action: Cediranib is a highly potent inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase activity, which inhibits VEGF-dependent angiogenesis, neovascular survival and vascular permeability.

How Supplied: Astra-Zeneca supplies and CTEP, NCI, DCTD distributes Cediranib. The agent

is available as beige film-coated tablets containing, 15 mg and 20 mg of AZD2171 free base. The,15 mg and 20 mg tablets are,7 mm and 8 mm in diameter, respectively. Each 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-25°C, (68-77°F)] and protect from light and moisture.

Stability: Stability studies are ongoing. Dispense 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 cediranib to controlled 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: Oral. Cediranib tablets should be taken either one hour before or two hours after meals.

Potential Drug Interactions: Cediranib (AZD2171) clearance is primarily mediated by flavin-containing monooxygenase enzymes (FMO1 and FMO3) and UGT1A4. It is not a substrate of CYP450 enzymes. In vitro studies suggest that cediranib (AZD2171) 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 cediranib (AZD2171) is a weak inhibitor of BCRP, Pgp, OATP1B1, OATP1B3, OCT2 and MATE1. Use caution in patients who are taking concomitant medications that are sensitive substrates of these transporters since there is a low potential for drug-drug interactions. *In vivo* studies show that cediranib (AZD2171) could increase exposure of drugs like metformin by inhibiting renal tubular transporter MATE2-K, but this is thought to be infrequent and mild in severity. Cediranib is not an inhibitor of OAT1 or OAT3.

In vitro studies using hepatic cultures show that cediranib (AZD2171) did not inhibit CYP 1A2, 2A6, 2C8, 2C9, 2C19 and 2E1 and showed no induction of CYP 1A2, 2B6 and 3A4/5. It did

weakly inhibit CYP 2D6 and 3A4/5, but this inhibition not expected to cause any clinically relevant drug interactions. The possibility that cediranib (AZD2171) may induce gastrointestinal CYP3A and UGT enzymes cannot be excluded; therefore, the efficacy of hormonal contraceptives may be reduced. Advise women study participants to use an additional non-hormonal contraceptive method.

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

Oral anticoagulants are not absolutely contraindicated during treatment with cediranib; however, use cediranib with caution and increase monitoring in patients while on study. Patients who receive VEGF inhibitors are at increased risk of bleeding and hemorrhage.

Patient Care Implications: Agents that inhibit VEGF signaling have the potential to affect wound healing; therefore, it is recommended that cediranib is stopped two weeks prior to elective surgery and restarted when the surgical wound has healed. Patients should be excluded from participating in clinical studies with cediranib if they have had recent (at least two weeks, or until any wound has completely healed) major thoracic or abdominal surgery prior to study start, or a surgical incision that is not fully healed.

Pre-clinical data indicate that cediranib 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 six (6) months after the last dose of cediranib. Male study participants should avoid fathering a child or donating sperm during the study and for six (6) months after the last dose of cediranib. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient. Refer to the protocol document for specific guidance.

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

Cediranib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3)

8.1.3 **Agent Ordering and Agent Accountability**

8.1.3.1 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.

Study agent must be ordered after patient is registered to the treatment arm as no starter supplies are available for this study.

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

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

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

8.1.3.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines:

http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.ci.nih.gov/iam/index.jsp
- CTEP 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 Bevacizumab

Chemical Name: Immunoglobulin G1 (human-mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer

Other Names: Avastin™, anti-VEGF monoclonal antibody, Anti-VEGF rhuMAb, rhuMAb-VEGF

CAS Registry Number: *216974-75-3*

Molecular Formula: $C_{6538}H_{10034}N_{1716}O_{2033}S_{44}$

Molecular Mass: 149,196.82 g/mol

Dilution: Withdraw appropriate dose of bevacizumab and dilute in 100mL of 0.9% sodium chloride. Bevacizumab is incompatible with dextrose solutions.

Mode of Action: Bevacizumab binds and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), thereby inhibiting VEGF-dependent angiogenesis, neovascular survival and vascular permeability.

How Supplied: Commercially available. Please refer to the FDA-approved package labeling for additional information.

The solution also contains α,α-trehalose dihydrate, monobasic monohydrate sodium phosphate, dibasic sodium phosphate, polysorbate 20 and water for injections.

Storage: Injection concentrate – store at 2 – 8 °C (36 – 46 °F) and protect from light and moisture. Do not freeze. Store diluted solution at 2 – 8 °C (36 – 46 °F) for up to 8 hours.

Route of Administration: IV infusion via a rate-regulating device per institutional guideline with associated pre-medications. Do not administer as an IV push or bolus. If no institutional

guidelines exist, follow below:

> Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer subsequent doses over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

Potential Drug Interactions: Oral anticoagulants are not absolutely contraindicated during treatment with bevacizumab; however, use bevacizumab with caution and increase monitoring in patients while on study. Patients who receive VEGF inhibitors are at increased risk of bleeding and hemorrhage.

Patient Care Implications: Agents that inhibit VEGF signaling have the potential to affect wound healing; therefore, it is recommended that bevacizumab is stopped four weeks prior to elective surgery and restarted when the surgical wound has healed. Patients should be excluded from participating in clinical studies with bevacizumab if they have had recent (at least four weeks, or until any wound has completely healed) major thoracic or abdominal surgery prior to study start, or a surgical incision that is not fully healed.

Availability
Bevacizumab is commercially available.

Agent Ordering
Bevacizumab will be ordered commercially.

8.3 Blood Pressure Cuffs

A patient who is randomized to the olaparib and cediranib treatment arm (Arm 1) will be given a blood pressure cuff. Blood pressure cuffs that are supplied for this study, are only to be used for this study.

Supply and Distribution: Blood pressure cuffs will be supplied by VWR and distributed by Biologics. Each kit contains a blood pressure monitor (which includes standard size cuff), an adaptor and a large size cuff. Kits will be shipped in the original manufacturer's packaging.

Ordering Instructions: No starter supplies are available. Sites are permitted to order a maximum of 10 Blood Pressure kits at a time for enrolled patients. To obtain the kits, please complete the "Shipment Authorization Form" and email to lisa.rutter@vwr.com. The form is available on the CTSU website. Please allow for 3 business days from requesting blood pressure kits until expected receipt. All orders will be shipped via FedEx Priority Overnight.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Specimen Requirements

Study	Assay	Required Specimen	Collection Time Points	Collection Details
Plasma Panel (Nixon Laboratory, Duke University)	Multiplex ELISA assay utilizing the Aushon Cirascan Imaging System	Two 4 mL tubes of blood	1.1.1.1.1 Baseline, day 1 of cycle 2, and at the time of progression or end of study	Collect in purple top tubes. Specimens should be processed on site to obtain plasma and then shipped on dry ice.
BROCA- HR (Dr Elizabeth Swisher, University of Washington)	BROCA Panel sequencing – a targeted capture and parallel sequencing approach using the SureSelectXT enrichment system on a Bravo liquid-handling instrument (Agilent)	7 mL whole blood	Baseline	Collect in yellow top (ACD solution A) tube. Specimen to be shipped at ambient temperature for overnight delivery.
		Archival FFPE slides (primary tumor)	Baseline	2 consecutive unstained 10 µm slides should be provided.
Whole Exome Sequencing (WES)	PicoGree®DNA quantitation (qPCR)	Archival FFPE slides (primary tumor), blood, *and/or* plasma	Baseline	One (1) H&E slide and twenty (20), 4 µm unstained air-dried plus slides OR One (1) or more core punches (minimum of 4 mm diameter) from tumor block Also, two 10 mL Streck

				tubes and one 10 mL EDTA tube of blood
Tumor Perfusion, pH and Oxygenation (Dr Elizabeth Gerstner, MGH)	Dynamic susceptibility MRI, ME-aCEST-SAGE-EPI		Baseline, prior to cycle 3 day 1 and then every 2 months	
Brain Tumor Cellularity (Dr Elizabeth Gerstner, MGH)	Diffusion MR imaging		Baseline, prior to cycle 3 day 1 and then every 2 months	

9.2 Integrated Correlative Studies

9.2.1 **Plasma Angiome Panel**

9.2.1.1 Collection of Specimens

Please refer to the Specimen Requirements table in Section 9.1. for details regarding specimen collection.

9.2.1.2 Handling of Specimens

Plasma samples will be analyzed by multiplex ELISA assays for plasma-based biomarkers utilizing the Aushon Cirascan Imaging System. The Aushon Cirascan Imaging System is used specifically for the imaging and analysis of chemiluminescent protein arrays in a 96-well plate. The protein arrays are created by spotting up to 16 different capture antibodies per well in each well of the 96-well plate. The advantage of this system is that multiple target proteins of interest can be analyzed at the same time reducing the amount of sample required for analysis. In brief, a small volume of sample and/or standard is added to each well of the 96-well plate resulting in the capture of the target proteins by the arrayed antibodies. Biotinylated antibodies are then added that specifically bind the captured target proteins. Streptavidin conjugated to HRP (horseradish peroxidase) is then added followed by a chemiluminescent substrate. Imaging of the plate is performed using Aushon Cirascan Imaging System. Protein concentrations in the samples are quantified by comparing the intensity of the spots in the unknown wells to standard curves. Samples should be processed on site to obtain plasma and then shipped on dry ice. Biomarker assays are time sensitive, and samples should be stored on ice and processed within four hours of collection. Instructions for processing and labeling samples are below:

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 (ie. whole blood, EDTA plasma, citrate plasma, serum, urine)

9.2.1.3 Shipping of Specimens

Please refer to the Specimen Requirements table in Section 10.1 for specific shipping requirements. 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, Research Drive
Durham, NC 27710

9.2.1.4 Site Performing Correlative Study

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

9.2.2 **BROCA testing**

9.2.2.1 Collection of Specimens

Please refer to the Specimen Requirement table in Section 9.1.

9.2.2.2 Handling of Specimens

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 germline and somatic mutations that influence response to therapy will be utilized. Library preparation has been fully automated to increase sample turnaround and lower cost. Paired-end libraries with 350bp inserts will be prepared from 1µg of constitutional or neoplastic DNA and hybridize to a custom pool of oligonucleotides targeting genomic regions as previously described using the SureSelectXT enrichment system on a Bravo liquid-handling instrument (Agilent). Following capture, samples will be barcoded with 48 different indexed primers. The pooled samples are sequenced on a single lane of a HiSeq flowcell (Illumina) with 2x101bp paired end reads and a 7bp index read to allow for de-multiplexing and binning of individual samples. Single nucleotide variants and insertions and deletions will be detected as previously described with some updates in the bioinformatics pipleline. Deletions and duplications of exons will be detected by a combination of depth of coverage and split read analysis as previously described, supplemented with additional alignments generated by SLOPE. 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 treatment on the trial.

9.2.2.3 Shipping of Specimens

Please refer to the Specimen Requirements table in Section 9.1. for specific shipping requirements.

Please ship to:

Mark Radke
University of Washington
1959 NE Pacific ST, HSB BB632
Seattle WA 98195
206-685-7927

9.2.2.4 Site Performing Correlative Study

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

9.2.3 **Whole Exome Sequencing (WES)**

9.2.3.1 Collection of Specimens

Please refer to the Specimen Requirement table in Section 9.1.

Tissue collected within 6 months prior to registration is preferred. Older specimens may be submitted, but the yield of nucleic acids may be lower, and characterization and analysis may be compromised.

Two 10 mL Streck tubes and one 10 mL EDTA tube of blood will be collected for analysis of germline DNA and banking of plasma for future cell free DNA (cfDNA) studies. Blood collections will be performed according to standard procedures and will be shipped to the ETCTN Biorepository with the tumor specimen

9.2.3.2 Oversight of Tumor Specimen Collection

For biospecimen collection, it is suggested, but not required, that a pathologist or qualified designee at the submitting institution assure the presence of tumor in solid tissue specimens and deem the biospecimen suitable for research with minimally 30% non-necrotic tumor content. If a pathologist or designee is not available at the submitting institution, the pathologist at the ETCTN Biorepository will assess tumor quantity and quality.

Alternatively, the pathologist of the submitting institution may confirm histopathology and histological characteristics of the biospecimen.

It is the responsibility of the submitting institution to provide only those biospecimens that are not necessary for diagnostic purposes.

9.2.3.3 Procedure to Recall Biospecimens for Diagnostic/Patient Care Purposes

If needed, residual tissue or blood that is currently stored in the biobank can be reclaimed. If DNA or RNA analysis is required, some or all specimens may be returned for documented diagnostic/patient care or medically necessary events, including a request by or on behalf of the patient for tissue to determine eligibility for enrollment in a research protocol/clinical trial. Accessioned specimens, extracted nucleic acids, or slides sent to a reference laboratory **cannot be reclaimed**.

The ETCTN Biorepository will need to be notified in writing of the specific reason for recalling the specimens as well as of what specimen types (*e.g.*, FFPE blocks) need to be returned. Investigators should use their local records to retrieve and provide the number of the specimen that needs to be returned.

A description of the extenuating circumstance(s) will be required to accommodate the recall request. Every effort will be made to facilitate medically necessary events or procedures to assure appropriate medical care for a patient with a serious or life-threatening illness. This does not cover patient issues related to needing or wanting genetic information or specimens for genetic testing for personal risk from germline or somatic findings.

9.2.3.4 Handling of Specimens

Processing of Biospecimens

Specimens received at the ETCTN Biorepository for molecular characterization analyses, such as WES, will be processed for DNA/RNA extraction as follows:

Tumor tissue received in formalin will be paraffin-embedded. All FFPE blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide, and for nucleic acid extractions, additional RNase-free slides.

Whole blood collected in Streck tubes will be centrifuged to separate PBMCs and plasma, and will be stored in a -80°C freezer.

DNA and RNA will be co-extracted from tumor tissue. DNA will be extracted from the whole blood collected in the EDTA tube. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of DNA and RNA will be shipped to the central sequencing laboratory for analysis.

Next Generation Sequencing

DNA and RNA libraries for WES and RNA-Seq will be generated at the central sequencing laboratories by standard procedures. Sequencing will be carried out on an Illumina 2500 sequencer, and these results will have variant calling through the procedures associated with the GDC. Results from these assays, annotated with limited clinical data (presentation, diagnosis, staging, summary treatment, outcome, *etc.*), will be stored in the Database of Genomes and Phenotypes (dbGaP) and in the GDC.

Banking and Use of Specimens in Future Research

Any biospecimens remaining after processing will be retained indefinitely at the ETCTN Biorepository under appropriate storage conditions. Specimen types may include:

- FFPE block
- PBMCs
- Plasma from Streck tubes (for future cfDNA analysis)
- Isolated nucleic acids

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the currently defined research studies, will be retained at the ETCTN Biorepository. Protocol-specified studies should be clearly described and prioritized in the protocol, and in general, should not require additional review and approval. Investigators are encouraged to consult with the ETCTN Biorepository for the evaluation of residual tissue specimens approaching depletion for protocol-specified studies.

Banked specimens may be distributed to investigators for laboratory research studies as specified in the protocol or after appropriate review of the proposed research studies by CTEP. In cases where additional clarification about laboratory research studies is needed, review and approval of a submitted analysis and data sharing plan by the NCI, ETCTN, CIRB, and if appropriate, the NCI Collaborator, may be needed.

If future use is denied or withdrawn by the patient, the samples will be destroyed and not used in any future study. Biospecimen recalls for patient issues related to needing/wanting genetic testing to determine personal risk from germline/somatic findings is not permitted (see Procedure to Recall Biospecimens).

The ETCTN Biorepository will not deplete a biospecimen unless written permission is received from the ETCTN Program Directors or designee. The investigator must provide a written proposal describing the nature of the research to be performed, the technical and analytical validation of the assays being used, the goals, objectives and statistical analysis plan for the research being performed. The investigators should submit this concept/proposal through the CTEP Protocol and Information Office (PIO). The proposal will be reviewed by the Medical Officer assigned to the protocol and will be reviewed by the CTEP Protocol Review Committee (PRC) for approval or disapproval for use of biospecimens that may be depleted.

Manual checks of minimal biospecimens may occur at the time of distribution to confirm the amount available in relationship to the amount requested by the researcher. Once minimal amounts are reached, the ETCTN Program Directors of the biospecimen resource is notified before specimens are distributed.

9.2.3.5 Shipping of specimens

Please refer to Appendix J for additional information on shipping of specimens.

Shipping Address

Ship the specimen collection to the address below using overnight courier (FedEx), early morning delivery option.

ETCTN Biorepository
Nationwide Children's Hospital
700 Children's Dr., WA1340
Columbus, OH 43205

Phone: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred. There is no central Courier account for this study. Sites are responsible for all costs for overnight shipment per sample shipment to the ETCTN Biorepository, utilizing the site screening and base intervention payments.

NOTE: The ETCTN Biorepository FedEx Account will not be provided to submitting institutions.

Contact Information for Assistance

For all queries, please use the contact information below:

ETCTN Biorepository
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

9.3 Imaging correlative studies (Tumor Perfusion and Oxygenation, and Brain Tumor Cellularity)

9.3.1 MRI Sequence Acquisition

For sites acquiring the advanced MRI scans will be performed with the same sequences during each visit, including T1- and T2-weighted volumetric images, fluid attenuated inversion recovery (FLAIR), diffusion imaging, perfusion scans, and a ME-aCEST-SAGE-EPI. The advanced scans will be done at sites capable of acquiring these sequences. All other sites should acquire the standard brain tumor protocol even if not participating in the advanced imaging. See Appendix F for aquisition parameters and scan transfer/shipment details.

10. STUDY CALENDAR

Screening assessments must be completed after consent and within 4 weeks of starting treatment, unless otherwise specified. On treatment days, assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

	Pre-Study[a]	Each cycle		Cycles 1 & 2 Weekly[b]	Cycle 2 D1	Odd numbered Cycles	Every 4 Cycles	Off Treatment[o]
		D1	D15					
Informed Consent[a]	X							
Medical History	X							
Concomitant Medications[c]	X	X		X				X
AE Assessment		X	X	X				X
Vital Signs[d]	X	X	X					X
BP measurement at Home[e]				Twice a day, or as directed by your doctor				
Physical Exam	X	X[a]						X
Height	X							
Weight	X	X	X					X
Performance Status (KPS) [f]	X	X[a]						X
CBC with differential	X	X[a]	X					X
Serum Chemistry[g]	X	X[a]	X					X
INR and PTT	X							
TSH and Free T4[h]	X	X[a]						X
Urine protein: creatinine ratio[i]	X	X[a]	X					X
EKG	X							
MUGA or ECHO[j]	X						X	
Pregnancy test[k]	X							
Tumor Measurements[l]	X					X		
Translational bloodwork[m]	X				X			X
Archival Tissue[n]	X							

[a] Informed consent will be obtained prior to any study-related screening tests and within 4 weeks of starting study drug. For Cycle 1 Day 1, physical examination and laboratory evaluations do

not have to be repeated if they have been performed at screening within 7 days of Cycle 1 Day 1.
[b] Patients should be contacted at least once weekly over the phone or be assessed in person for the first two cycles on study to assess for AEs and concomitant medications.
[c] Because of a potential for interaction of cediranib and olaparib with other drugs through the cytochrome P450 system, special attention should be paid to other medications known to affect P450 isoenzymes, in particular CYP3A4.
[d] Temperature, pulse rate, blood pressure
[e] Relevant only for participants in Arm 1. Please refer to section 5.3 for information on blood pressure monitoring
[f] See Appendix A for KPS performance status
[g] Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, phosphorus, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin.
[h] Pre-study, prior to the first 2 cycles, and at off-study visit for all participants. Otherwise, should be checked prior to each cycle if clinically indicated.
[i] Urinanalysis may be used instead. See Section 6.2.5 for Management of Proteinuria.
[j] MUGA or echocardiogram should be done at baseline and every 4 cycles for those patients at increased risk for compromised LVEF. Increased risk patients have had one or more of the following: (1) prior treatment with anthracyclines, (2) prior treatment with trastuzumab, (3) NY Heart Association classification of II, (4) prior central thoracic RT, (5) history of myocardial infarction within the 12 months prior.
[k] beta-HCG for women of childbearing potential.
[l] Tumor measurements by MRI will be performed within the 2 weeks prior to starting study treatment, prior to cycle 3 day 1 (- 1 week), and every 8 weeks (+/- 1 week) thereafter of treatment. If a partial or complete response is noted, a confirmatory CT scan or MRI should be performed. The next planned restaging MRI may be used as the confirmatory scan. All standard MRIs should be performed according to Appendix F.
[m] Bloodwork will be drawn for translational studies of plasma angiome at baseline (pre-treatment), at Cycle 2 day 1 of treatment and at the time of progression/end of study. Bloodwork will be drawn for BROCA-HR study at baseline only. Participation in these translational studies is required for study participation. Details on the required specimens are found in Section 9. Patients may choose to opt out of translational bloodwork at the time of progression.
[n] Archival tissue – Please refer to section 9.1 for specimen requirenments. Please refer to section 9.2.2 for information regarding handling and shipping of specimens. Archival tissue may be collected and shipped after study initiation.
[o] Off-treatment assessments should be performed within 30 days of stopping study treatment.

11. MEASUREMENT OF EFFECT

11.1 Definition of Measurability of Disease (per Response Assessment in Neuro-Oncology (RANO) Criteria)

All lesions are to be measured at each evaluation; however, if there are too many measurable lesions, choose the largest two to be followed before a patient is entered on study.

Evaluable for objective response: only those patients who have measurable disease present at baseline and have received at least one dose of therapy will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Measurable disease: Bidimensionally, contrast-enhancing, measurable lesions with clearly defined margins by MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm.

Non-measurable evaluable disease: Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 1 cm.

11.2 Response Assessments

Response assessments will be performed every two months on treatment using the objective status categories per RANO criteria, which, in addition to radiographic scans, comprise elements of the neurological exam, KPS, and steroid use. Response assessments are to be derived from baseline or Best Response (see below). If a partial or complete response is noted, a follow up confirmatory CT scan or MRI should be performed.

11.2.1 **Best Response**

This will be calculated from the sequence of objective status. For patients who are having all disease sites assessed at every evaluation period, the best response will be defined as the best objective status, measured according to Section 12.2.2. If the response does not persist at the next routinely scheduled scan, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, e.g. still present on the subsequent scan, it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the subject does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.

11.2.2 **Objective Status (per RANO Criteria)**

11.2.2.1 Complete Response (CR). All of the following criteria must be met:

a. Complete disappearance of all enhancing measurable and non-measurable disease

sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No new lesions
c. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
d. Patients must be on no steroids or on physiologic replacement doses only.
e. Stable or improved non-enhancing (T2/FLAIR) lesions
f. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related.

11.2.2.2 Partial Response (PR). All of the following criteria must be met:

a. ≥ 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No progression of non-measurable disease.
c. No new lesions.
d. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e. The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of steroid compared to baseline scan.
g. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related.

11.2.2.3 Progressive Disease (PD). The following criteria must be met:

a. 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response or baseline if no decrease) on stable or increasing doses of steroids
and/or one or more of the following:
b. Significant increase in T2/FLAIR non-enhancing lesion on stable or incrasing doses of steroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (radiation therapy, demylination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
c. Any new lesions
d. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection etc.). The definition of clinical deterioration is left to the discresion of the investigator but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered

neurologic deterioraton, unless attributable to co-morbid events or changes in steroid dose.

e. Failure to return for evaluation due to death or deteriorating condition.

11.2.2.4 Stable Disease (SD). All of the following criteria must be met:

a. Does not qualify for CR, PR, or PD.
b. All measurable and non-measurable sites must be assessed using the same techniques as baseline.
c. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of steroids compared to baseline scan. In the event that the steroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the steroid dose was equivalent to the baseline dose.
d. Stable clinically.

11.2.2.5 Unknown Response Status. Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

These RANO Response Criteria are also summarized in the following table.

Table 11-1: Summary of the RANO Response Criteria

	CR	**PR**	**SD**	**PD[#]**
T1-Gd+	None	≥ 50% decrease	< 50% decrease - < 25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for Response	All	All	All	Any*

[#] Progression occurs when any of the criteria with * is present.
NA: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

11.2.3 **Efficacy Assessments**

11.2.3.1 Progression-Free Survival (PFS) is defined as the time from randomization to the earlier of progression or death due to any cause. Patients alive without disease progression are censored at date of last disease evaluation.

11.2.3.2 Overall Survival (OS) is defined as the time from randomization to death due to any cause or censored at date last known alive.

11.2.4 **Response Review**

Radiographic response to treatment will be determied locally by the treating physician. All brain MRI images may be collected in the future for consideration of central review at a later time point.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

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

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

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

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

12.2 Data Reporting

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

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

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

12.2.1 **Method**

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

12.2.2 **Responsibility for Data Submission**

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

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

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

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

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

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

12.3 Collaborative Agreements Language

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

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

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

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

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

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

12.4 Genomic Data Sharing Plan

The investigators and statistician and/or bioinformaticians for a study will have access to all data on mutations and variants stored in the Theradex Data Base and the GDC. This information will be sequestered from access throughout the study until it is analyzed for purposes of reporting and publishing of the study results. As specified in the CRADA for the agents used in the clinical study, the pharmaceutical collaborator will have at least 6 months, longer if needed for a regulatory filing, to review the data and or receive copies of the data once the study is completed and analyzed, or sooner, if specified for purposes of generating Intellectual Property. Once these timeframes have been exceeded, the data will be available through a Data Access Committee (DAC) in the GDC following NCI and Collaborator review of the proposals.

12.5 Incidental/Secondary Findings Disclosure Procedure

Given the potential clinical implications conferred by detecting a germline and/or somatic mutation in one of the proven cancer susceptibility genes, this protocol will use the following disclosure procedure, consistent with the recommendations of the American College of Medical

and Genomics (ACMG) (Green *et al*., 2013 and Kalia *et al.,* 2016):

The NCI Molecular Characterization Laboratory will review the mutations/variants once at the time of initial specimen evaluation according to the most recent version of the ACMG guidance on variants. The NCI Molecular Characterization Laboratory will not re-review all specimens received if a new version of the ACMG guidance is published after the initial review.

For each participant with a pathogenic or likely pathogenic germline and/or somatic variant detected in the WES of blood (as defined in the ACMG guidance), the NCI Molecular Characterization Laboratory will report to the Program Director or Scientific Officer the UPID and variant(s) identified. The Program Director or Scientific Officer will contact Theradex to obtain the name of the protocol, investigator treating the patient, and the Principal Investigator of the grant. The treating physician will be contacted by phone and in writing to ask the patient whether he or she is interested in learning more about the finding.

If the patient wants to know more, the physician should contact the Program Director for more information about the mutation/variant. The treating physician and a medical genetics counselor should meet with the patient to discuss the importance and meaning of the finding, but not the finding itself, and notify the patient that this research finding must be confirmed by Sanger sequencing at the patient's/patient insurer's expense in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory. The treating physician and genetic counselor should inform the patient of the confirmed result and its meaning and significance to the patient. If desired, the patient may elect to undergo genetic counseling and confirmatory CLIA-approved clinical testing on his or her own. Neither the research laboratory nor the National Cancer Institute will be responsible for the costs incurred for any confirmatory genetic testing or counseling.

13. STATISTICAL CONSIDERATIONS

The purpose of this study is to compare the efficacy and safety of the combination of olaparib and cediranib with bevacizumab in patients with recurrent glioblastoma (GBM) and to evaluate integrated biomarkers and imaging correlates as predictors of tumor response to this combination regimen.

13.1 Study Design/Endpoints

The primary objective of this study is to determine whether cediranib/olaparib combination (experimental arm) will improve the progression-free survival at 6 months (PFS6) compared to bevacizumab alone (control arm) in patients with recurrent GBM.

In this randomized phase 2 trial, patients with recurrent GBM who meet inclusion criteria will be randomized to Arm 1 (cediranib / olaparib combination) or Arm 2 (bevacizumab) in a 1:1 ratio.

The doses of cediranib and olaparib are as determined in a phase I trial by Liu et al.

Information about known prognostic molecular markers of the disease, such as MGMT methylation and IDH mutation, will be collected from each participating site as these studies are now routinely performed at the time of the initial diagnosis. It is not planned to repeat these tests, unless indicated. Age, KPS, and resection type also have prognostic value in overall survival.

Analysis population will be based on the modified ITT population. Patients who did not receive any study treatment will be excluded from analysis

Primary endpoint is PFS6, defined as the proportion of subjects in the analysis population who remain progression-free for at least six months from randomization.

Secondary endpoints include:

- Overall survival (OS) and treatment adverse events.
- Circulating cytokines involved with angiogenesis (bFGF, Ang-1, Ang-2, Tie-2, SDF1-α, Collagen IV, PlGF, sVEGFR1, sVEGFR2, VEGF, Il-1β, Il-6, Il-8, TNF-α, CAIX)
- Serial circulating biomarkers involved with DNA repair
- Tumor genomic alteration by whole exome sequencing
- Imaging correlates (vascular permeability, tumor perfusion and oxygenation, brain tumor cellularity)

13.2 Sample Size/Accrual Rate

On the basis of data reported by Friedman et al the progression-free survival at 6 months with bevacizumab alone was assumed to be approximately 40%. With 35 patients in each arm, there will be at least 85% power to detect an increase in PFS6 rate from 40% to 63% at a one-sided

significance level of 0.1 using the Log-Rank test and assuming a total study duration of 20 months.

We anticipate a monthly accrual rate of 5-7 patients therefore an estimated total study duration of 20 months. A minimum of 52 events will be required in order to conduct the final analysis. In accordance with NIH policy, both men and women of all races and ethnic groups are eligible for this study. We will also analyze treatment differences by gender, race, and ethnicity. The following table lists the projected accrual for each racial and ethnic group based upon previous NCI recurrent GBM trials

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	0	1	0	0	**1**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	4	7	1	2	**14**
White	15	28	2	7	**52**
More Than One Race	0	0	1	2	**3**
Total	**19**	**36**	**4**	**11**	**70**

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13.3 Stratification Factors

No stratification factors will be applied to randomized patients.

13.4 Interim Analysis

An early futility monitoring will be conducted when 50% of total information is collected. If at this stage the observed HR favors the control arm, the study will be stopped for futility.

13.5 Analysis of Primary and Secondary Endpoints

For the primary endpoint, PFS6 will be calculated with the Kaplan-Meier method and the Log-Rank test will be conducted to compare between the study arms. 95% CI will be provided for proportion outcomes

Time to event analysis such as OS and PFS will be calculated with the Kaplan-Meier method and the Log-Rank test will be conducted to compare between the study arms. Time to event will be calculated from start of treatment until documentation of event. For OS analysis, patients still alive will be censored at their last date of follow-up. For PFS analysis, patients without progression will be censored at their last date known to be progression free. OS analysis will be conducted within 2 years from start of study. It is expected that at least 80% of the study population have died within this time frame. 95% CI will be provided for all rate and proportion outcomes (such as response rate). ORR will be calculated as the proportion of patients that are determined to be CR, PR or SD at 2, 4, 6 and 12 months out of the total enrolled. Exact binomial 95% CI will be provided for this rate.

Descriptive statistics will be provided for all continuous Biomarkers outcomes, Contingency tables will be provided for categorical data. All comparisons between study arms will be adjusted for multiplicity and in particular FDR (Hochberg and Binaymini) will be used for genome data. Binary endpoints, including maximum grade AE during treatment, will be reported using 95% binomial confidence intervals.

Sequential boundaries will be used to monitor dose-limiting toxicity rate. The accrual will be halted if excessive numbers of dose-limiting toxicities are seen, that is, if the number of dose-limiting toxicities is equal to or exceeds b_n out of n patients with full follow-up (see table). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.05 when the rate of dose-limiting toxicity is equal to the acceptable rate 0.4.

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	-	-	5	6	7	7	8	8	9	10	10	11	11	12	12	13	13	14
Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	14	15	15	16	16	17	17	18	18	19	19	20	20	21	21					

This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 0.4, using a one-sided level 0.015602 test.

13.5.1 Advanced Imaging Analysis

Date will be analysed as per the methods of Gerstner et al, 2016.

The DSC data will be analyzed using NordicIce or a similar program to generate values for rCBV and rCBF.

Our goal is to explore the association of changes from baseline vascular MRI parameters at one month from initiation of treatment, with PFS in participants of this trial. Correlation between parameters will be assessed using Pearson correlation. Kaplan–Meier survival estimates for PFS time will be generated with its 95% confidence interval (CI). The ROC curves for the imaging markers will be constructed for PFS-6. The areas under the ROC curves (AUC) will be estimated empirically with the trapezoid rule. The 95% CI of the AUCs will be calculated using Delong method (Delong et al, 1988).

13.6 Reporting and Exclusions

13.6.1 **Evaluation of Toxicity**

All participants who receive at least one dose of cediranib, olaparib or bevacizumab will be evaluable for toxicity from the time of their first treatment. Toxicities will be graded via CTCAE 4.0 until March 31, 2018. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018

13.6.2 **Evaluation of Response**

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

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

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

reported. The 95% confidence intervals should also be provided.

14. PUBLICATION PLAN

The results should be made public within 12 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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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: CYP3A4 INDUCERS AND INHIBITORS

NOTE: The displayed lists are for reference only and reviewers should consult a frequently updated medical reference for the most current list of agents with CYP interactions.

CYP3A4 Inducers (prohibited)

Armodafenil[1]	Modafinil[2]	Primidone[1]
Barbiturates[2]	Nafcillin[1]	Rifabutin
Bosentan[1]	Nevirapine	Rifampin
Carbamazepine	Oxcarbazepine	Rifapentine[1]
Efavirenz	Pentobarbital[1]	St. John's wort[2]
Fosphenytoin[1]	Phenobarbital	Troglitazone[3]
	Phenytoin	
	Pioglitazone[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.
[3] Weak inhibitor per Lacy et al. May be used with caution.
Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

CYP3A4 Inhibitors

Strong Inhibitors (prohibited)	**Moderate Inhibitors** (avoid if possible; reduce olaparib dose if use unavoidable)	**Weak Inhibitors** (use with caution, avoid if possible)
Amprenavir[1]	Amiodarone[1]	Chloramphenicol[2]
Atazanavir[1]	Aprepitant	Ciprofloxacin[2]
Clarithromycin	Cimetidine[1]	Diethyldithiocarbamate[2]
Conivaptan[1]	Clotrimazole[1]	Fluvoxamine[2]
Delavirdine[1]	Cyclosporine[1]	Gestodene[2]
Fosamprenavir[1]	Desipramine[1]	Mibefradil[2]
Fospropofol[1]	Doxycycline[1]	Mifepristone
Imatinib[1]	Efavirenz[1]	Norfluoxetine[2]
Indinavir	Erythromycin	Star fruit[2]
Isoniazid[1]	Fluconazole	Troleandomycin[2]
Itraconazole	Fosaprepitant[1]	
Ketoconazole	Grapefruit juice	
Miconazole[1]	Haloperidol[1]	
Nefazodone	Lidocaine[1]	
Nelfinavir	Metronidazole[1]	

Nicardipine[1] Posaconazole[1] Propofol[1] Quinidine[1] Ritonavir Saquinavir[2] Telithromycin	Norfloxacin[1] Sertraline[1] Tetracycline[1] Verapamil Voriconazole[1]	

[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 C: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARDS

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.

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

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

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

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

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

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

June 2016

STUDY DRUG INFORMATION WALLET CARD

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

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

  and can be contacted at _____.

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements The patient _____ is enrolled on a clinical trial using the experimental study drug, **olaparib (AZD2281).** This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

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

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

- The enzymes in question are CYP 3A4/5, 1A2, 2B6, 2C9, 2C19 and UGT1A1. Olaparib is cleared by CYP3A4/5 and is affected by strong and moderate inhibitors and inducers of CYP3A4/5. Olaparib inhibits CYP3A4 and UGT1A1enzymes and may increase levels of other drugs that are cleared by these enzymes. Olaparib induces CYP 1A2, 2B6 and 3A4 enzymes and has the possibility of inducing CYP 2C9, 2C19 enzymes that may result in decreased levels of other drugs that are cleared by these enzymes.

The transport proteins in question are P-glycoprotein (P-gp), organic anion-transporting polypeptides (OATP1B1 and OAT3), organic cation transporters (OCT1 and OCT2), multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and breast cancer resistance protein (BCRP). Olaparib requires P-gp to move in and out of cells and concomitant administration of strong P-gp inhibitors and inducers should be avoided. Olaparib inhibits P-gp, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K transporters and has the possibility of inducing P-gp and that may affect the transport of other drugs that depend on these proteins to move in and out of cells. Use caution when taking substrates of these transporters, such as statins.

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

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

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

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

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

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit, grapefruit juiceand 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

_____.

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: PATIENT PILL DIARY

Today's Date _____ Cycle Number _____

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 a EXAMPLE ROW for how to complete this diary.

CEDIRANIB Take _____ (number) _____ mg tablets once a day. Take on an empty stomach 1 hour before taking the morning dose of olaparib.					**OLAPARIB** Take ____ (number) ____ mg and ____ (number) ____ mg tablets twice a day 12 hours apart after a light meal. Tablets should be taken with 8 ounces of water.					
Day	**Date**	**15 mg**	**20 mg**	**AM**	**Day**	**Date**	**100mg**	**150mg**	**AM**	**PM**
1	*1/1/16*	*2*	*0*	*7:00*	*1*	*1/1/16*	*2*	*0*	*8:00*	*8:00*
1										
2										
3										
4										
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28										

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

APPENDIX E: PATIENT'S BLOOD PRESSURE DIARY

Today's Date _____ Cycle Number _____

Patient Name_____ Patient Study ID_____

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

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

Patient's Signature: _____ Date: _____

Date of this clinic visit:_____

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

APPENDIX F: MRI PROTOCOL

REQUIRED CONSENSUS MRI AQUISITION PARAMETERS (STANDARD IMAGING PROTOCOL) For sites that do NOT have advanced imaging available: (*FDA/NBTS/NCI Standardized MRI Protocol*).

The MRI acquisition protocols defined in the following table have been defined by an international consensus panel. These parameters have been reviewed and adopted by the National Cancer Institute (NCI) and the Federal Drug Administration (FDA), and these acquisition parameters are required for all national and FDA drug-registration trials. The specific acquisition parameters, the sequence of imaging acquisition, and the plane of imaging are all **required** as explicitly stated in these protocols. Additionally, individual patients must be consistently imaged at the same field strength as their baseline registration scan. *Additional sequences that the site wants can be added prior to injection or after the 3DT1 post but the time between injection and the 3DT1 post must be the same for each scan. For example, susceptibility weighted imaging or T1 post with thicker sections are often included in brain tumor MRIs and those can be added.*

All MRI scans for every patient for the duration of the study, regardless if site is participating in the advanced MRI protocol, should be sent to Dr. Ben Ellingson. To ensure that the MRI protocol is being followed, Site Qualification will be performed by UCLA. New sites ideally will send a phantom scan prior to their first patient. Alternately, he first patient scan should be submitted for review within 2 weeks of the scan, and before the patient receives their second protocol scan. Sites will receive a notification of approval with the qualification results once complete.

Future scans may be batched shipped every 3 months or sent as they are acquired to ensure no scans are missed. The preferred method for submitting scans is through a secure FTP. To set up an image transfer account, please contact Dr. Ellingson and Catalina Raymond. Please see Imaging transfer manual for additional details.

- Ben Ellingson: Bellingson@mednet.ucla.edu
- Catalina Raymond: CRaymond@mednet.ucla.edu

If unable to submit via FTP, sites may send MRIs on CD/DVD. Please anonymize scans and label with patient's study ID and date of the scan. Send to:

UCLA brain tumor imaging laboratory
Center for computer vision and imaging biomarkers
924 Westwood Blvd
Suite 615
Los Angeles CA 90024
310-482-7572

MRIs should include all sequences acquired (ex. SWI or thicker T1 post images), be anonymised

prior to sending and labeled with the patient's study ID and date of scan. Even unscheduled, emergently aquired MRIs should be sent particularly if the scan indicates progressive disease.

3T Protocol:

	Ax FLAIR	Ax DWI	3D T1 Pre		Ax T2	3D T1 Post[b]
Sequence	TSE[c] – (turbo dark fluid)	EPI[f]	MPRAGE[d,e]		TSE[c]	MPRAGE[d,e]
Plane	Axial	Axial	Axial/Sagittal		Axial	Axial/Sagittal
Mode	2D	2D	3D		2D	3D
TR [ms]	>6000	>5000	2100[g]		>2500	2100[g]
TE [ms]	100-140	Min	Min		80-120	Min
TI [ms]	2500		1100[h]			1100[h]
Flip Angle	90/≥160	90/180	10-15	**Contrast Injection [a]**	90/≥160	10-15
Frequency	≥256	128	256		≥256	256
Phase	≥256	128	256		≥256	256
NEX	≥1	≥1	≥1		≥1	≥1
Frequency Direction	A/P	R/L	A/P		A/P	A/P
FOV	240mm	240mm	256mm (for 1mm isotropic)[i]		240mm	256mm (for 1mm isotropic)[i]
Slice Thickness	3mm	3mm	1mm[i]		3mm	1mm[i]
Gap/Spacing	0	0	0		0	0
Diffusion Options		*b* = 0, 500, and 1000 s/mm^2				
Parallel Imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x
Scan Time (Approx)	4-5 min	3-5 min	5-8 min		3-5 min	5-8 min

[a] 0.1 mmol/kg or up to 20cc (single, full dose) of MR contrast.

[b] Post-contrast 3D axial T1-weighted images should be collected with identical parameters to pre-contrast 3D axial T1-weighted images

[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)

[d] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).

[e] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.

[f] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and

therefore should be used only if EPI is not an option.

[g] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.

[h] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.

[i] FOV and matrix size should be chosen to keep resolution at 1mm isotropic voxel size. Note that all voxel measurements should be equal in x, y, and z dimensions.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view

1.5T Protocol:

	Ax FLAIR	Ax DWI	3D T1 Pre		Ax T2	3D T1 Post[b]
Sequence	TSE[c] – (turbo dark fluid)	EPI[f]	MPRAGE[d,e]		TSE[c]	MPRAGE[d,e]
Plane	Axial	Axial	Sagittal/Axial		Axial	Sagittal/Axial
Mode	2D	2D	3D		2D	3D
TR [ms]	>6000	>5000	2100[g]		>3500	2100[g]
TE [ms]	100-140	Min	Min		100-120	Min
TI [ms]	2200		1100[h]			1100[h]
Flip Angle	90/≥160	90/180	10-15		90/180	10-15
Frequency	≥256	128	≥172		≥256	≥172
Phase	≥256	128	≥172		≥256	≥172
NEX	≥1	≥1	≥1		≥1	≥1
Frequency Direction	A/P	R/L	A/P		A/P	A/P
FOV	240mm	240mm	256mm (for ≤1.5mm isotropic)[j]		240mm	256mm (for ≤1.5mm isotropic)[j]
Slice Thickness	≤4mm	≤4mm	≤1.5mm[j]		≤4mm	≤1.5mm[j]
Gap/Spacing	0	0	0		0	0
Diffusion Options[i]		*b* = 0, 500, and 1000 s/mm^2				
Parallel Imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x
Scan Time (Approx)	4-5 min	3-5 min	5-8 min		3-5 min	5-8 min

Contrast Injection [a]

[a] 0.1 mmol/kg or up to 20cc (single, full dose) of MR contrast.

[b] Post-contrast 2D axial T1-weighted images should be collected with identical parameters to pre-

contrast 2D axial T1-weighted images

[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)

[d] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).

[e] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.

[f] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.

[g] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.

[h] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.

[i] Older model MR scanners that are not capable of >2 *b*-values should use $b = 0$ and 1000 s/mm^2.

[j] FOV and matrix size should be chosen to keep resolution *less than* 1.5mm isotropic voxel size. Note that all voxel measurements should be equal in x, y, and z dimensions.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view

ADVANCED MRI PROTOCOL: ANATOMIC + PERFUSION

	3D T1w Pre	Ax 2D FLAIR	Ax 2D DWI		DSC Perfusion[h]	Ax 2D T2w	3D T1w Post[b]
Sequence	IR-GRE[d,e]	TSE[c]	EPI[f]		GE-EPI	TSE[c]	IR-GRE[d,e]
Plane	Sagittal/Axial	Axial	Axial		Axial	Axial	Axial/Sagittal
Mode	3D	2D	2D		2D	2D	3D
TR [ms]	2100[g]	>6000	>5000		1500	>2500	2100[g]
TE [ms]	Min	100-140	Min		25-35	80-120	Min
TI [ms]	1100[h]	2500					1100[h]
Flip Angle	10º-15º	90º/≥160º	90º/180º		60º	90º/≥160º	10º-15º
Frequency	256	≥256	128		128	256	256
Phase	256	≥256	128		128	256	256
NEX	≥1	≥1	≥1		>120 Reps; Inject after 45s of baseline data (>30 time points)	≥1	≥1
FOV	256mm	240mm	240mm		240mm	240mm	256mm
Slice Thickness	1mm	3mm	3mm		5mm	3mm	1mm

Pre-Load Contrast Injection [a]

Gap/Spacing	0	0	0		0-5mm	0	0
Options/Notes			*b* = 0, 500, and 1000 s/mm^2 ≥3 directions		Cover tumor; 18-20 Ga IV, right arm; 3-5 mL/sec inj. rate		
Parallel Imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 2x
Scan Time (Approx)	5-8 min	4-5 min	3-5 min		3 min	7 min	5-8 min

[a] 0.05 mmol/kg (1/2 dose) preload should be injected 1-2 minutes prior to DSC MRI acquisition.
[b] Post-contrast 3D T1-weighted images should be collected with equivalent parameters to pre-contrast 3D T1-weighted images
[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
[d] FL2D = two-dimensional fast low angle shot (FLASH; Siemens) is equivalent to the spoil gradient recalled echo (SPGR; GE) or T1- fast field echo (FFE; Philips), fast field echo (FastFE; Toshiba), or the radiofrequency spoiled steady state acquisition rewound gradient echo (RSSG; Hitachi). A fast gradient echo sequence without inversion preparation is desired.
[e] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[f] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[g] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option. Further, this type of acquisition takes considerable more time.
[h] 0.05 mmol/kg dose injection at a rate of 3-5cc/sec. Maximize slice coverage to include the entire lesion as well as normal brain to the skull vertex. The posterior fossa can be excluded from coverage if there are not enough slices to cover the entire brain.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; SS-EPI = single-shot echo planar imaging; GE-EPI = gradient echo echo planar imaging; 2DFL = two-dimensional FLASH (fast low angle shot) gradient recalled echo; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view; TE = echo time; TR = repetition time; TI = inversion time; PD = proton density; DSC = dynamic susceptibility contrast

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	5 mg daily	20 mg daily	40 mg daily	Yes, but not CYP450
	Rarely used: **Perindopril**	**4 mg daily**	**None**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **Quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	Losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 and 2C9 substrate
	Candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	Irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	Telmisartan	**40 mg daily**	**None**	**80 mg daily**	**Yes, but not CYP450**

	Valsartan	**80 mg daily**	**None**	**160 mg daily**	**Yes, but not CYP450**
Selective β Blockers (BB)	Metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	Atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	Acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	Bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	CYP 3A4 substrate
α and β Blocker	Labetalol	100 mg twice daily	200 mg twice daily	400 mg twice daily	Yes, but not CYP450
Diuretics	Hydralazine	10 mg four times daily	25 mg four times daily	50 mg four times daily	No
	Hydrochlorothiazide	12.5 mg AM daily	25 mg AM daily	50 mg AM daily	No
	Furosemide	20 mg daily	20 mg twice daily	40 mg twice daily	No
Nitrates	Isosorbide dinitrate ER	40 mg daily	40 mg twice daily	80 mg twice daily	CYP 3A4 substrate
	Isosorbide mononitrate ER	30 mg AM daily	60 mg AM daily	90 mg AM daily	CYP 3A4 substrate
Dihydro-pyridine Calcium-channel Blockers (DHP CCB)	Nifedipine XL	30 mg daily	60 mg daily	90 mg daily	CYP 3A4 substrate
	Amolodipine	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: NEW YORK HEART ASSOCIATION CLASSIFICATIONS

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

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

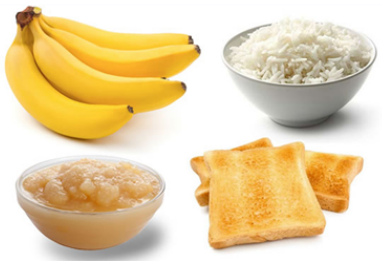
***** To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks

APPENDIX I: PATIENT HANDOUT

Patient Handout: Management of Diarrhea

# of loose bowel movements	What to do
< 4	Take 1 loperamide (Imodium) after each loose bowel movement. Drink Fluids. If your diarrhea gets wore, call your study team. Do not take more that 8 loperamide (Imodium) in 24 hours.
4 - 6	Take 1 loperamide (Imodium) after each loose bowel movement. Drink Fluids. Start BRAT diet If your diarrhea gets wore, call your study team. Do not take more that 8 loperamide (Imodium) in 24 hours.
> 6	Call your study team

B anana
R ice
A pple
T oast



APPENDIX J: COLLECTION OF SPECIMENS

*Collection procedures described in this Appendix J apply to the **ETCTN Biobanking and Molecular Characterization Initiative** (WES) only*

Blood Sample Collection

Whole blood samples will also be collected into 1 EDTA (purple-top) tube (10 mL) and 2 cell-free DNA (cfDNA) Streck tubes (2 × 10 mL) to obtain plasma/peripheral blood mononuclear cells (PBMCs).

Collection in EDTA (purple top) Tubes

Collect blood in EDTA tube, and gently invert 5-10 times to mix. Maintain specimens at ambient temperature (room temperature) during collection and transport. Blood (10 mL) collected in an EDTA (purple top) tube will be processed for plasma and DNA per the standard operating procedure (SOP).

Collection in Streck Tubes

Collect blood in two cfDNA Streck tubes (10 mL), Cat No. 218992, and invert to mix. **Note: blood must be thoroughly mixed to ensure preservation of specimen.** After collection, blood in cfDNA Streck tubes **should never be refrigerated**, as this will compromise the specimen. Blood in cfDNA Streck tubes is stable at room temperature. These tubes will be shipped to the ETCTN Biorepository for further processing. Upon receipt at the ETCTN Biorepository, blood in cfDNA Streck tubes will be processed for plasma and DNA per the SOP**.**

APPENDIX K: TRACKING OF SPECIMENS

Tracking procedures described in this Appendix K apply to the ***ETCTN Biobanking and Molecular Characterization Initiative*** *(WES)*

Tracking of Specimens

All biospecimens collected for this trial must be submitted using the ETCTN Rave Specimen Tracking System (STS) unless otherwise noted. The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository. Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.

Important: Failure to complete required fields in STS may result in a delay in sample processing. Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

Overview of Process at Treating Site

OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF**:** Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date on each label.
- After collection, store labeled specimens as described in Section 9.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have PHI data like name, mailing address, medical record number or SSN redacted. Do not redact SPID, block number or relevant dates.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form**:** Enter Collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF**:** Enter tracking number, your contact information, recipient, number of containers and ship date once for the 1st specimen in a shipment.
- **Copy Shipping** CRF**:** Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

APPENDIX L: SHIPPING OF SPECIMENS TO THE ETCTN BIOREPOSITORY

*Shipping procedures described in this Appendix L apply to the **ETCTN Biobanking and Molecular Characterization Initiative** (WES)*

Shipping to the Biobank

Tissue may be shipped in batches Monday through Wednesday, since the ETCTN Biorepository does not need to perform additional time-sensitive pre-analytic processing on them.

Labeling of Specimens

Tissue samples are to be labeled with:

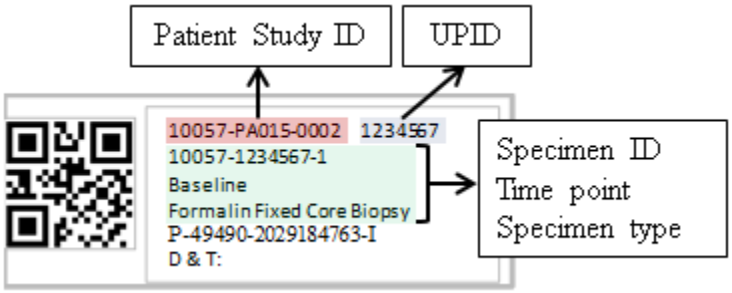
- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, FFPE Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)

Blood samples are to be labeled with:

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date (to be added by hand)

Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

Packing Instructions

The shipment of all human tissue samples must comply with appropriate regulations as specified by the carrier. Frozen samples should be sent on dry ice. At a minimum, all samples must be packaged within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture resistant (*e.g.*, cardboard mail tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers.

1. Before packaging specimens verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed and wrapped in parafilm.
2. Place samples into a biohazard envelope with absorbent material and seal the envelope securely.
3. Place the biohazard envelope into a Tyvek envelope and seal securely.
4. Place the sample(s) and a copy of the shipping manifest and corresponding pathology report (when applicable) into the insulated shipping container.
5. Place the lid on top of the container. Close the outer flaps and tape shut.
6. Attach a shipping label to the top of the shipping container.
7. Place an Exempt Human Specimen sticker to the side of the container.
8. Ship samples via overnight courier (FedEx preferred) to the address listed below.

Additional notes for specimen shipping

Include a cold (not frozen) pack when shipping specimens during hot weather. In winter months, please include extra insulation, such as bubble wrap inside the shipping container, to prevent specimens from freezing.

When shipping slides, first place them in a plastic slide holder and stabilize by placing cotton or soft paper under the lid. Tape the lid so that is does not pop open during shipment (one piece of tape is sufficient).

Forms to be Included in specimen shipping

Copies of the following forms and reports are required to be included with all submissions of pathology materials:

- The pathology report(s) on tumor from the most recent pre-diagnostic biopsy or surgery specimen(s).

IMPORTANT NOTE: Corresponding anatomical clinical pathology report **MUST** be submitted with the specimen for central confirmation of histology, or the sample will not be processed. This can be a prior pathology report on the same malignancy.

- Reports on immunologic, immunohistochemical, or molecular studies, if performed on the pre-trial materials
- A completed Sample Submission Form. This form is to be submitted with tissue collected for research only
- The Sample Tracking System (STS) generated shipping manifest

NOTE: The pathology report for the submitted biopsy material, if pathology review was performed locally, is required to be uploaded into Rave as soon as it is available.

Shipping Address

Ship the specimen collection to the address below using overnight courier (FedEx), early morning delivery option.

ETCTN Biorepository
Nationwide Children's Hospital
700 Children's Dr., WA1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred. There is no central Courier account for this study. Sites are responsible for all costs for overnight shipment per sample shipment to the ETCTN Biorepository, utilizing the site screening and base intervention payments.

NOTE: The ETCTN Biorepository FedEx Account will not be provided to submitting institutions.

Contact Information for Assistance

For all queries, please use the contact information below:

ETCTN Biorepository
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

APPENDIX M: ASSAY INFORMATION

Assays described in this Appendix M apply to the ***ETCTN Biobanking and Molecular Characterization Initiative****.*

Next-generation sequencing assays (whole exome sequencing [WES] will be performed at the Molecular Characterization Laboratory on the purified DNA and RNA aliquots provided by the ETCTN Biorepository.

DNA libraries will be generated using the Agilent SureSelect XT Target Enrichment System, and quantitated via digital droplet PCR (ddPCR). Library samples are denatured, diluted and clustered on the cBot clonal amplification system in preparation for sequencing on the Illumina HiSeq 2500.