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TO: ALL SWOG MEMBER, NCORP

FROM: Dawne Wenzel, M.A., Protocol Coordinator (dwenzel@swog.org)

RE: **S0905**, "A Phase I/Randomized Phase II Study of Cediranib (NSC # 732208) versus Placebo in Combination with Cisplatin and Pemetrexed in Chemonaive Patients with Malignant Pleural Mesothelioma" Study Coordinators: Drs. A.S. Tsao, N.J. Vogelzang and I.I. Wistuba.

REVISION #10

Study Coordinator: Anne S. Tsao, M.D.
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IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
  (√) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
(√) Other: Changes to drug information section

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice. If local approval is not granted within 30 days, accrual must be suspended until approval is obtained.

***Sites not using the NCI CIRB**:* Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. The changes in this revision are effective upon approval by the local IRB; however, any changes to eligibility become effective 6 weeks after distribution of this notice. If local approval is not granted within 6 weeks, accrual must be suspended until approval is obtained.

REVISION #10

This revision is in response to a Request for Rapid Amendment (RRA) from Dr. S. Percy Ivy (ivyp@ctep.nci.nih.gov), Dr. James Zwiebel (ZwiebelJ@CTEP.NCI.NIH.gov), and Dr. Meg Mooney (mooneym@ctep.nci.nih.gov).

The above-referenced protocol has been revised as follows:

1. The Version Date of the protocol and Model Consent Form have been updated.

2. **Page 13, Section 3.1b**: CAEPR Version 2.13 (September 29, 2016) has replaced CAEPR Version 2.11 (November 10, 2011).

   - The SPEER grades have been updated.

   - **Added New Risk:**
     - **Also Reported on Cediranib Trials But With Insufficient Evidence for Attribution: Acidosis; Activated partial thromboplastin time prolonged; Allergic reaction; Alopecia; Aspiration; Ataxia; Atrial fibrillation; Atrial flutter; Avascular necrosis; Bloating; Blood and lymphatic system disorders - Other (polycythemia); Blurred vision; Bone marrow hypocellular; Capillary leak syndrome; Cardiac disorders - Other (premature ventricular complexes); Cardiac disorders - Other (valvular heart disease); Cardiac troponin I increased; Central nervous system necrosis; Chills; Cholecystitis; Chronic kidney disease; Cystitis noninfective; Delirium; Depression; Dermatitis radiation; Duodenal ulcer; Ear and labyrinth disorders - Other (ears feel full/plugged); Edema face; Ejection fraction decreased; Esophageal necrosis; Esophageal ulcer; Eye disorders - Other (blindness); Eye disorders - Other (visual disturbance); Febrile neutropenia; Flushing; Gait disturbance; Gastric necrosis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (hydrops); Gastrointestinal disorders - Other (tongue sensitivity); Gastroesophageal reflux disease; Hemoglobin increased; Hydrocephalus; Hypomagnesemia; Hypothermia; INR increased; Intestinal stoma leak; Investigations - Other (elevated ammonia level); Ischemia cerebrovascular; Malaise; Menorrhagia; Metabolism and nutrition disorders - Other (failure to thrive); Mobitz (type) II atrioventricular block; Muscle weakness left-sided; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (muscle cramps); Musculoskeletal and connective tissue disorder - Other (rotator cuff injury); Myositis; Neck pain; Nervous system disorders - Other (coma); Nervous system disorders - Other (right hemiparesis); Olfactory nerve disorder; Oral cavity fistula; Palpitations; Pancreatitis; Papilledema; Pericardial effusion; Pericarditis; Periodontal disease; Peritoneal necrosis; Photophobia; Pulmonary edema; Pulmonary fistula; Pulmonary hypertension; Rash acneiform; Restrictive cardiomyopathy; Retinal vascular disorder; Sinus bradycardia; Sinus pain; Sinus tachycardia; Skin and subcutaneous tissue disorders - Other (petechiae); Skin and subcutaneous tissue disorders - Other (plantar warts); Small intestinal obstruction; Stroke; Supraventricular tachycardia;**

Syncope; Tremor; Urinary tract obstruction; Urticaria; Vaginal fistula; Vascular Disorders- Other (hemorrhage), Vasculitis; Venous injury; Vertigo; Wound complication; Wound dehiscence

- **Increase in Risk Attribution:**
  - **Changed to Likely from Less Likely: Nausea; Voice alteration**
  - **Changed to Less Likely from Also Reported on Cediranib Trials But With Insufficient Evidence for Attribution: Alkaline phosphatase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased**

- **Decrease in Risk Attribution:**
  - **Changed to Also Reported on Cediranib Trials But With Insufficient Evidence for Attribution from Less Likely: Hyperthyroidism; Investigations - Other (increased blood erythropoietin); Seizure**

- **Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:**
  - **Added: Proteinuria**

- **Provided Further Clarification:**
  - **Bronchopulmonary hemorrhage, Epistaxis, Hepatic hemorrhage, Intracranial hemorrhage, and Rectal hemorrhage (under Also Reported on Cediranib Trials But With Insufficient Evidence for Attribution) are now reported as Vascular disorders - Other (hemorrhage) (under Less Likely).**

  - **The following footnote #2 was added: "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."**

  - Gastrointestinal disorders - Other (abdominal abscess) (under Also Reported on cediranib Trials But With Insufficient Evidence for Attribution) is now reported as Infection

The following changes have been made to the Model Consent Form. Because this study is closed to accrual, sites are not required to update their informed consent.

1. The version date has been updated.

2. **Page 6:** The "What side effects or risks can I expect from being in the study?" section has been changed to adhere to NCI Consent Form Template (Version May 2013) wording.

3. **Page 8:** The "risks and side effects related to the cediranib/placebo treatment we are studying" section has been modified to a condensed risk profile table of possible side effects for cediranib and categories of risk have been renamed. "Likely" is now "Common, Some May Be Serious," "Less Likely" is now "Occasional, Some May Be Serious," and "Rare but Serious" has been changed to "Rare and Serious."

   - **Increase in Risk Attribution:**
     - **Changed to Common from Occasional: Changes in voice; Nausea**
       - Changed to Occasional from Also Reported on cediranib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Bruising, bleeding

   - **Decrease in Risk Attribution:**

- Changed to Also Reported on cediranib Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Seizure

- **Changed for clarity:**

  - **"High blood pressure" has been changed to "High blood pressure which may cause blurred vision" in the Likely/Common category.**

  - **"Sores in internal organs which may cause rectal pain or throat pain" has been added in the Occasional/ Less Likely section and irritation or sores in the lining of the anus, mouth, rectum, voice box, throat, windpipe, and small bowel have been removed.**

  - **"Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place such as the lung" has been changed to "blood clot which may cause swelling, pain, shortness of breath" in the Occasional/Less Likely category.**

  - **"Progressive necrosis (tissue death) of a part (the white matter) of the brain without inflammation (swelling an redness" and "abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings ((RPLS)" has been changed to "Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) in the Rare, and Serious/Rare but Serious Category.,**

- **Removed:**

  - **In the Less Likely/Occasional Category: Abnormally high level of thyroid gland hormone, abnormally low level of thyroid gland hormone, increased blood level of a liver enzyme (ALT/SGPT), increased blood level of a liver enzyme (AST/SGOT), increased levels of a substance involved in the production of red blood cells, increased levels of a substance (thyroid stimulating hormone) involved in the function of the thyroid gland, which indicated an underactive thyroid, more protein leaking in to the urine than usual, often a sign of kidney disease, decreased blood level of phosphate, convulsion,**

  - **In the Rare but Serious/ Rare, and Serious category: Decrease in heart's ability to pump blood during "active "phase of the heartbeat (systole), and blood clot in a blood vessel (artery)/**

- **Added:**

  - **Bruising and bleeding have been added to the Occasional Category.**

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to cediranib is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activation Date: March 15, 2010

SWOG

A PHASE I/RANDOMIZED PHASE II STUDY OF CEDIRANIB (NSC #732208) VERSUS PLACEBO IN COMBINATION WITH CISPLATIN AND PEMETREXED IN CHEMONAIVE PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

PARTICIPANTS: PHASE I: ALL SWOG APPROVED PHASE I INSTITUTIONS AT: UNIVERSITY OF ARIZONA, BROOKE ARMY MEDICAL CENTER, CITY OF HOPE, CLEVELAND CLINIC, COLUMBIA, LOYOLA, MD ANDERSON, MEDICAL UNIVERSITY OF SOUTH CAROLINA, UNIVERSITY OF NEW MEXICO, PSOC-SWEDISH MEDICAL CENTER, USC NORRIS CANCER CENTER, UC DAVIS, UNIVERSITY OF COLORADO, UNIVERSITY OF KANSAS, UNIVERSITY OF KENTUCKY, UNIVERSITY OF MICHIGAN, UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO, UNIVERSITY OF WASHINGTON, WAYNE STATE UNIVERSITY, SCOTT AND WHITE HOSPITAL, HIGHLAND ONCOLOGY GROUP

PHASE II: The Phase II portion of the study will be open to ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS active effective 9/16/11.

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AGENTS:

CTEP-supplied:
Cediranib/Placebo (Recentin™, AZD2171)
(NSC 732208; CTEP IND #72,740)

Commercially available:
Cisplatin
Pemetrexed (Alimta™)

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TABLE OF CONTENTS

SCHEMA

Phase I portion (open to limited institutions as listed on the Title Page):

Registration

↓

6 cycles of pemetrexed + cisplatin + cediranib
at assigned dose level (see Section 7.4), followed by maintenance cediranib

↓

Temporary closure to assess
the dose for Phase II

Phase II portion (open to all SWOG institutions):

Registration/Randomization

↓

6 cycles of pemetrexed
and cisplatin
+
cediranib or placebo,
followed by maintenance cediranib/placebo

A patient may be enrolled to either the Phase I portion or the Phase II portion, not both.

1.0 OBJECTIVES

This study will be conducted in two different parts:

1.1 Phase I Portion

a. To establish the MTD and the recommended Phase II dose of cediranib in combination with cisplatin and pemetrexed.

b. To assess the safety and toxicity of the regimen.

1.2 Phase II Portion

c. To assess whether cisplatin/pemetrexed plus cediranib as compared to cisplatin/pemetrexed plus placebo improves progression-free survival in patients with malignant pleural mesothelioma.

d. To compare overall survival in patients treated with cisplatin/pemetrexed plus cediranib to those treated with cisplatin/pemetrexed plus placebo.

e. To assess the safety and toxicity profile of the regimen.

f. To assess response rate (confirmed and unconfirmed, complete and partial responses) and disease control rate (response or stable disease) in the subset of patients with measurable disease by RECIST criteria.

g. To assess response rate and disease control rate using modified RECIST criteria for pleural tumors in the subset of patients with measurable disease by modified RECIST criteria for pleural tumors.

h. To assess the rate of agreement between local and central pathology review of mesothelioma and its histologic subtypes.

i. To collect specimens for banking for use in future research studies.

2.0 BACKGROUND

Malignant Mesothelioma

Unresectable malignant mesothelioma is a challenging disease that has a poor response to chemotherapy. *(1)* Historically, treatment with chemotherapy leads to a median time to progression between 3 to 4 months. *(2-3)* The current standard frontline regimen in unresectable mesothelioma is cisplatin-pemetrexed which yields a 12.1 month median overall survival and 5.7 month median time to progression. *(2)* Although this regimen was an advance in mesothelioma treatment, there are associated toxicities and survival results remain grim. A new paradigm in treatment is needed with identification of new targets of therapy and novel combination regimens.

Inhibition of malignant tumor angiogenesis is establishing itself as an important aspect of cancer therapy. This field of work needs to be further developed in malignant mesothelioma as it is well established that mesothelioma cells secrete and express angiogenic factors such as vascular endothelial growth factor (VEGF) and receptor (VEGFR) and platelet derived growth factor (PDGF) and receptor (PDGFR). *(4-8)*

Cediranib

Cediranib (Recentin™, AZD2171 (NSC 732208), an orally available small molecule, is a potent inhibitor of receptor tyrosine kinases (RTKs), which influence the effects of a key angiogenic factor, vascular endothelial growth factor-A (VEGF). VEGF is implicated in tumor blood vessel formation and in disease progression in a wide range of solid tumor malignancies. Expression of this factor is increased by diverse stimuli which include proto-oncogene activation and hypoxia, with the hypoxic state frequently occurring in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature and thereby potentially contributes to tumor progression – a leaky tumor endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumor cell migration during metastasis. With the goal of suppressing neovascularization and thus inhibiting tumor growth and metastasis, numerous antiangiogenic agents have been developed. In contrast to many of these intravenously-administered antiangiogenic agents, a recently emerging class of novel orally-administered VEGF TK inhibitors including cediranib has been developed. *(9-11)*

Two high-affinity receptors for VEGF with associated TK activity have been identified on human vascular endothelium, KDR (kinase insert domain-containing receptor = VEGFR2) and Flt-1 (fms-like tyrosine kinase 1 = VEGFR1). Although the relative contributions of KDR and Flt-1 signaling in mediating tumor progression have not been elucidated, a number of studies suggest that KDR performs a predominant role. Cediranib is a potent inhibitor of both KDR (IC_{50} < 0.002 microM) and Flt-1 (IC_{50} = 0.005 microM) and shows activity versus c-kit, platelet-derived growth factor receptor beta (PDGFRβ), and Flt-4 at nanomolar concentrations, but is selective against other serine/threonine kinases studied. It has been shown that cediranib potently and selectively inhibits VEGF-stimulated human umbilical cord vascular endothelial cell (HUVEC) proliferation with an IC_{50} of 4 nM. *(12)* These authors have also demonstrated the agent's profound inhibitory effect on vessel area, length, and branching at subnanomolar concentrations using a modified fibroblast/endothelial cell co-culture system. Cediranib's effects on hemodynamic parameters have been studied in an athymic rat xenograft model of human colorectal carcinoma (SW620) using perfusion-permeability dynamic contrast-enhanced magnetic resonance imaging. (pp-DCE-MRI) *(13)* This method clearly demonstrated that in this model, cediranib significantly reduced vascular permeability by 80% ($P<0.005$) and vascular volume by 68% ($P<0.05$).

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 orally (PO) at doses from 0.75 to 6 mg/kg/day (2.25-18 mg/m^2/day) in a constant volume of 0.1 mL/10 g body weight for 24-28 days. Cediranib produced a statistically significant inhibition of tumor growth in all human tumor types examined when dosed at 1.5 mg/kg/day (4.5 mg/m^2/day) or higher.

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. *(14)* 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. *(15)* When dosed with cediranib (0.75 to 6 mg/kg/day PO) at the time early lesions start to develop, the number of tumor foci was not affected, but their growth was inhibited. When tumors were well-established 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 non-clinical efficacy of cediranib can be found in **Section 4.1** of the investigator's brochure.

Nonclinical Pharmacology and Toxicology

Nonclinical pharmacology and toxicology company-sponsored cediranib studies have been conducted in rats, dogs, and cynomolgus monkeys. In rats and dogs, oral bioavailability is high, but absorption is relatively slow, with peak plasma concentration (C_{max}) of the agent seen 4-6 hours after PO dosing. Plasma concentrations and exposure are generally linear over the dose ranges studied in rats. Cediranib is excreted in the feces (> 70% of the dose) of rats, dogs, and cynomolgus monkey after both PO and intravenous administration. Fecal excretion was the predominant route of elimination (> 70% of the dose) in both rat, dog and cynomolgus monkey after both oral and intravenous 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 oral dose indicated that systemic exposure increased in a greater than dose-proportional manner over the dose range 0.05 to 2.5 mg/kg.

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

VEGF has three major biological activities in endothelial cells of rats and primates of the age groups used in the nonclinical studies. 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 to 60% reduction in CYP1A activity at the 2.5 mg/kg dose level. Inhibition studies in vitro using human hepatic microsomal protein gave IC_{50} values for cediranib against CYP2D6, CYP3A4 testosterone, and CYP3A4 midazolam of 32.9, 16.2, and 21.4 mcg/mL, respectively. For CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1, the IC_{50} values were outside the concentration range of cediranib examined. As the clinically relevant plasma concentration of cediranib has not yet been determined, any possible effect on compound clearance and drug interaction is currently unknown.

Further details of the nonclinical pharmacology and toxicity of cediranib can be found in **Sections 4.2 and 4.3** of the investigator's brochure, respectively.

Clinical Studies

The safety, tolerability, efficacy, and pharmacokinetics (PK) of cediranib are currently being evaluated in three Phase I monotherapy studies in patients with solid tumors and metastatic liver disease (Study 2171IL/0001), in relapsed or refractory acute myeloid leukemia (Study 2171IL/0002), and in elderly patients with metastatic prostate adenocarcinoma (Study 2171IL/0003). In addition, an ongoing company-sponsored Phase I study is currently assessing

the safety and tolerability of cediranib in combination with gefitinib (IRESSA™) in patients with advanced cancer (Study 2171IL0004). A detailed description of the preliminary data from these studies is provided **in Section 5** of the investigator's brochure.

In Study 2171IL/0001, patients have received cediranib at doses ranging from 0.5 to 60 mg. Patient cohorts receive a single dose of cediranib followed by a 7-day washout period then start a 28-day cycle of daily doses of the agent at the same dose level they received initially. The company reports that preliminary safety data from this study show that cediranib appears to be well tolerated at doses up to and including 45 mg/day. The 60 mg dose of cediranib appears to be less well tolerated and is associated with increased adverse events, dose interruptions, and increases in serum thyroid stimulating hormone (TSH). The most frequently reported adverse events (AEs) in Study 2171IL/0001 were fatigue (13/36 [36%]), nausea (13/36 [36%]), diarrhea (10/36 [28%]), and vomiting (10/36 [28%]). Three serious adverse events (SAEs) including an abnormal liver function test, hypertension, and hypoglycemia were considered to be related to cediranib. The company reported that the patients reporting the incidences of hypertension and hypoglycemia recovered, while the patient with an abnormal liver function test improved while on trial. Increases in mean arterial blood pressure (MAP) were observed for at least one time point in several patients across all of the cediranib doses studied. No clinically relevant changes in electrocardiogram parameters, heart rate, or laboratory parameters have been observed. The company reports that while only limited and preliminary safety data are currently available from the other three studies, those data also suggest that cediranib is well tolerated.

Preliminary cediranib PK data from two ongoing Phase I clinical studies (Study 2171IL/0001 and 2171IL/0003) have established that following a single dose, cediranib is orally available with C_{max} ranging from 1 to 8 hours post dosing. Concentrations declined in an apparent bi-exponential manner thereafter with a $t_{½lz}$ ranging from 12.5 to 35.4 hours. Steady-state plasma concentrations were predicted by the single dose PK with the grand arithmetic mean temporal change parameter value being 1.07. This observation supports the concept that there are no time-dependent PK changes. Dose proportionate increases in C_{max}, $C_{max,ss}$, AUC, and AUC_{ss} provide no evidence to reject linear PK for single and multiple cediranib doses ranging from 0.5 to 60 mg. The PK profile of cediranib supports once-daily oral dosing.

Initial assessments from the ongoing Phase I study in patients with solid tumors and metastatic liver disease (Study 2171IL/0001) have produced encouraging indications of potential biological efficacy in the patient population studied. Reductions in blood flow in hepatic metastases have been detected by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), and initial biomarker assessments (VEGF and VEGF-R2) have been encouraging. In addition, the company reports that one ovarian cancer patient had a minor-partial response in lung and liver metastases, while a colorectal cancer patient had a minor response.

Based on evidence from animal data with cediranib (vascular and renal pathology) and results in the ongoing Phase I clinical studies, it is possible that the agent will produce hypertension in man. Because hypertension seen in animals has been abrogated by nifedipine, the change is thought to be mechanistically related to inhibition of VEGF signaling, although a direct toxicologic effect on the blood vessels and kidneys cannot be ruled out. The potential for hypertensive changes following cediranib administration is additionally supported by evidence from use of other antiangiogenic agents in the clinic. For these reasons, patients should be monitored frequently for changes in blood pressure and renal function (blood urea nitrogen, creatinine, and urinary protein). The potential for myocardial injury indicates that patient levels of troponin T or troponin I should also be measured.

Certain physiologic processes other than endothelial cell growth are dependent on VEGF signaling, so inhibition of that growth factor may have implications for use of cediranib in selected patient populations. Pediatric studies with cediranib should be undertaken with caution because the agent increases the zone of hypertrophy in the epiphyseal growth plates thus preventing ossification during long bone growth. Cediranib interferes with normal reproductive processes

and completely prevents fetal development in rats at a dose of 2.5 mg/kg/day. For this reason, women of childbearing potential should have a negative pregnancy test before treatment with cediranib is initiated. In rat studies, cediranib significantly inhibited endochondral ossification and corpora lutea formation. *(16)*

VEGF/VEGFR in mesothelioma

VEGF is a peptide that promotes angiogenesis via induction of vascular permeability/ proliferation and endothelial migration. *(17-19)* Inhibiting VEGF/VEGFR pathway in the treatment of other malignancies has been shown to improve clinical outcome. *(20-22)* VEGF is likely to be an important target in malignant mesothelioma as the tumor cells secrete and express the VEGF ligand and receptor. *(5)* In vitro studies have suggested a VEGF autocrine loop via tyrosine kinase activation which promotes mesothelioma cell line proliferation. *(6,23)* These laboratory findings are translated into clinical observations as patients with elevated serum VEGF levels have increased microvessel density in their mesothelioma tumors and an overall worse clinical prognosis. *(6-8,24)*

One recent Phase III trial, which combines chemotherapy (cisplatin, gemcitabine) with or without bevacizumab (monoclonal antibody targeting VEGF) presented at ASCO 2007 showed no improvement in survival for the patients receiving bevacizumab for the overall population of mesothelioma patients. *(24-25)* However, patients with lower baseline levels of VEGF appeared to do better (in terms of PFS, OS) when they were treated with the chemo + bevacizumab. This is *highly* suggestive that bevacizumab was ineffective in mesothelioma because it could not counteract the high levels of VEGF in these patients; and therefore, VEGFR tyrosine kinase inhibitors which target the receptor may potentially be more potent in this population of patients than is bevacizumab which targets only the ligand VEGF and not the receptor.

PDGFR in mesothelioma

PDGF/PDGFR are found on vascular endothelial cells and promote angiogenic activity consisting of recruitment of pericytes to capillaries, promotion of smooth muscle cells in vessels, and formation of mesangial cells in the renal system. *(26-27)* Mesothelioma tumor cells secrete and express both PDGF-BB and PDGFRβ and may utilize this pathway for autocrine stimulation. *(4,28-32)* PDGF acts as a mitogen in vitro and murine xenografts of mesothelioma cells and cell line experiments show that inhibiting PDGF/PDGFR pathway can prevent mesothelioma cell proliferation. *(4,33-34)* PDGF/PDGFR have also been reported to have a role in regulating tumor vascular interstitial fluid pressure and transport of molecules, i.e. increase chemotherapy uptake into tumors. *(26,35-36)*

Targeting VEGFR and PDGFR simultaneously in mesothelioma

Targeting both VEGFR and PDGFR in mesothelioma is a reasonable strategy. Angiogenesis in malignant conditions yields disordered vasculature that is dependent on VEGF/VEGFR. It is hypothesized that more mature blood vessels are less dependent on VEGF possibly due to pericyte coverage, which can be regulated by PDGF/PDGFR. *(19,37-38)* Given that an autocrine loop effect may be present in malignant mesothelioma cells, it is feasible that targeting both pathways may provide additive cytostatic activity.

To date, few agents that target VEGF/VEGFR and PDGF/PDGFR have been used in clinical trials in mesothelioma. In a Phase II trial, imatinib mesylate (PDGF-R tyrosine kinase inhibitor) yielded a 16% disease stabilization rate > 3 months in pretreated advanced mesothelioma patients. *(39)* CALGB has sponsored two trials that target both VEGFR and PDGFR. CALGB 30107 is a Phase II trial using dual tyrosine kinase inhibitor vatalanib (PTK787). *(40)* This trial reports preliminary results (n=47) of 44.9% progression-free survival (PFS) rate at 3 months and median PFS 2.66 months. At IMIG 2006, the Phase II trial (CALGB 30307) using sorafenib at 400 mg twice daily in chemo-naïve or previously treated pemetrexed patients had a Grade 3-4 side effect profile inclusive of 25% fatigue and 13% hand-foot syndrome. *(41)* The overall response rate was 4.4%

with a 38.8% disease stabilization rate, median failure-free survival 4.1 months, and median overall survival 10.4 months. Patients who were chemo-naïve had worse survival outcomes compared to the pretreated patients. This trial did not meet its primary endpoint, but correlative studies are underway to determine which patients may have clinical benefit from the drug.

Sunitinib (targeting VEGFR, PDGFR, c-Kit, Flt-3) has been evaluated in a Phase II single arm trial in patients who had failed one platinum-pemetrexed regimen. Of 22 evaluable patients, there was a 15% partial response rate and 55% stable disease by modified RECIST criteria. In patients without a talc pleurodesis, ten were evaluated by FDG-PET and a 30% metabolic response (defined as a decrease in SUV levels) was seen. The median OS was 5.9 months, time to progression 3.5 months. There was one treatment related death attributed to pulmonary infiltrates and respiratory failure. *(42)*

Rationale for combining cisplatin, pemetrexed and cediranib

Cediranib (Recentin™, AZD2171)

Cediranib is a potent inhibitor of human receptor tyrosine kinases VEGFR-1, -2, -3, PDGFR-α and –β, c-Kit. Cediranib acts by inhibiting the tyrosine kinase activity of VEGF receptors, hereby disrupting the VEGF signaling pathway in endothelial cells. *(16)* Due to its low toxicity profile, available biologic targets, and oral availability, this antiangiogenic agent is an ideal therapy to investigate in patients with unresectable malignant mesothelioma in combination with front-line chemotherapy.

Cediranib has already been evaluated in Phase I trials (D8480C00003, D4840C00023) at 6 different dose levels (1, 2.5, 5, 10, 20, and 30 mg). After a single dose, cediranib is orally available with a t_{max} ranging from 2 to 8 hours post dosing with a median of 2 hours. Steady state levels after multiple oral doses is achieved after 7 days or repeat oral daily dosing. At 30 mg daily dosing after 28 days of consecutive oral administration, the t_{max} was 3 hours. Additional trials (D8480C00001) determined the MTD of cediranib to be 45 mg oral daily dose. The most frequently observed AEs were fatigue (56.6%), diarrhea (47%), nausea (41%), dysphonia (36%), hypertension (34.9%), vomiting (31.3%), and anorexia (28.9%).

Cediranib has been evaluated in a Phase I trial (D8480C00008) in combination with different chemotherapy agents (Investigator's Brochure 16 February 2007). Preliminary PK data obtained after a 28-day oral daily dosing with cediranib (10, 20, and 30 mg) in combination with pemetrexed. The most common AEs in the pemetrexed + 30 mg cediranib (n=8) were diarrhea (Grade 2 – 25%), nausea (Grade 2 – 12.5%), fatigue (Grade 1 – 50%), headache (Grade 1 – 62.5%), hypertension (Grade 2 – 50%), and rash (Grade 1 – 25%).

The preliminary data suggests that the 30mg dose of cediranib is safe and tolerable in combination with chemotherapy. Cediranib is being combined with platinum based doublets (carboplatin-paclitaxel, cisplatin-gemcitabine, FOLFOX6).

Preliminary results do not demonstrate significant additional toxicity at the 30 mg daily dose in combination platinum based therapies.

Combination of cisplatin and pemetrexed with cediranib

The chemotherapeutic agents to be combined with cediranib proposed in this trial consist of cisplatin and pemetrexed. Cisplatin is a platinum agent with an unclear metabolic pathway. It is believed that the chloride ligands of the cisplatin complex are displaced by water, forming positively charged platinum complexes. Cisplatin and platinum products are highly bound to tissue and plasma proteins, including albumin, γ-globulins and transferrin. Pemetrexed is a novel antifolate antimetabolite with broad spectrum activity against cancer cell lines. This agent inhibits a combination of several main folate-dependent enzymes including TS, DHFR and GARFT. In preclinical animal models, the major route of elimination was renal with 52% + 20% of total dose

eliminated as the parent drug. Preliminary results from clinical studies show that the primary route of elimination for pemetrexed is by urinary excretion of parent drug (up to 90% of administered dose). Additionally, in vitro studies predicted that pemetrexed would not cause clinically significant inhibition of other agents metabolized via CYP 450 enzyme system including CYP3A, CYP2D6, CYP2C9 and CYP1A2. However, there was a 21% inhibition noted with the CYP3A isoenzyme. These preclinical studies were done at very high concentrations of pemetrexed (885-1,000 μM) and the current dose of pemetrexed administered to patients would only be expected to reach 500 μM.

Rationale for combining cisplatin, pemetrexed and cediranib in Phase I/II study design

Based on prior research with the combination of pemetrexed and cediranib, there does not appear to be any evidence of an interaction between pemetrexed and cediranib. Also, cediranib combined with platinum-based doublets have not demonstrated significant antagonistic interaction. However, it is unclear if there will be any drug-drug interactions between the combination of the 3 agents cediranib, cisplatin and pemetrexed based on prior published data. Given the preliminary evidence, we plan on establishing the MTD and evaluating the safety and toxicity profile in a de-escalation Phase I study. Once the MTD is established, we will proceed with a Phase II randomized trial comparing the triplet combination regimen with cisplatin/pemetrexed plus placebo.

SWOG's Phase I Experience

In the first cohort with the cediranib 30 mg dose, one patient only received 4 days of cediranib during Cycle 1 and was not evaluable for DLT. This patient misunderstood instructions and only took 4 days of cediranib during Cycle 1. An additional two patients reported Grade 3 fatigue and one of these patients also reported Grade 3 diarrhea. Although technically, this did not reach the formal stopping rule (3 or more of the first 6 patients with a DLT), the Lung Committee leadership and treating investigators felt that the 30 mg cediranib dose was difficult for patients to continue as two of the six patients required dose reductions to 20 mg of cediranib during Cycle 1. In the 7 patients in Cohort 1, six patients completed at least 6 cycles of the triplet regimen and five had nine or more cycles of therapy. The median number of cycles from Cohort 1 is 10 cycles with four patients currently remaining on cediranib maintenance therapy. The most common toxicities associated with therapy during Cycle 1 included: Grade 2-3 fatigue, GI symptoms (Grade 1-2 anorexia, Grade 1-2 constipation, Grade 1-2 nausea, Grade 2 vomiting), Grade 1-2 lymphopenia, and one episode each of Grade 2 insomnia, Grade 2 hypertension, and Grade 1 myelosuppression. When assessing all cycles of therapy there were six reports of Grade 3 toxicity: 2 diarrhea, 2 fatigue, 1 lymphopenia, and 1 weight loss. The most common Grade 1-2 toxicities during all cycles of therapy included: GI complaints (abdominal pain, anorexia, constipation, diarrhea, nausea, vomiting), fatigue, hypomagnesemia, lymphopenia, and neutropenia. There were three cases of Grade 2 hypertension.

In the second cohort of patients, there were thirteen that started with cisplatin + pemetrexed + cediranib 20 mg daily. One patient received only thirteen doses of cediranib during Cycle 1 due to a scheduling problem with drug shipment (this has since been resolved) and was not evaluable for toxicity. In total, eleven patients currently remain on treatment. In Cycle 1, there were two patients that experienced DLTs with two Grade 3 events: dehydration and hyponatremia. The most common toxicities experienced in Cycle 1 include: Grade 1-2 fatigue, Grade 1-2 GI symptoms (anorexia, diarrhea, nausea, vomiting, and weight loss), Grade 1-2 hypomagnesemia, Grade 1-2 myelosuppression. There was one report each of the following Grade 1 or 2 toxicity: alopecia, anemia, peripheral edema, hypertension, GERD, headache, hiccups, hyperglycemia, hyperuricemia, hypokalemia, oral pain, thrombocytopenia, presyncope, proteinuria, and rash. For all cycles of therapy to date, there have been an additional ten reports of Grade 3 toxicity: 1 anemia, 1 constipation, 1 dehydration, 1 diarrhea, 1 hypertension, 1 mucositis, 1 nausea, 1 myelosuppression, 1 pulmonary hypertension, and 1 vomiting episode. One Grade 4 episode of thrombocytopenia has been reported and one Grade 5 report occurred. This patient with the

Grade 5 toxicity died after Cycle 3 of the triplet therapy – this patient is suspected to have a septic event with associated hypotension and delirium. In the initial AE report, the patient was mistakenly graded as Grade 5 encephalopathy and this has since been amended to "nervous system disorder – altered mental status".

Based on the twenty patients who have been treated with cisplatin-pemetrexed-cediranib, the study team has been encouraged by the preliminary efficacy results and the acceptable toxicity profile with the cediranib at 20 mg daily.

Pharmacogenetic Analyses

Knowledge of variation in kdr/flk-1 (the target of cediranib) as well as other genes in this pathway will assist in the interpretation of biomarker data. The proteins encoded by these other genes are either biomarkers themselves (VEGF-A) or they regulate the expression of biomarkers (HIF1α microvessel density). Additionally, other genes regulated by this pathway include candidates for genetic factors predisposing to the development of hypertension in response to anti-angiogenic therapy.

Two common (> 10% allele frequency) variants of the kdr/flk-1 gene were discovered and validated by an AstraZeneca polymorphism screen and have subsequently been reported in public domain data bases. Both of the polymorphic amino acid residues (Val/Ile 297; Gln/His 472) are located in the external domain of the receptor. Single nucleotide polymorphisms have also been described in the promoter region of the kdr/flk-1 gene and may correlate with expression levels of the receptor. While somatic mutations in the kdr/flk-1 gene have been described in colorectal tumors, there are no data on the functional consequences of these mutations and there are no reports of mutations in the kdr/flk-1 gene in other tumor types. *(43)*

Although no decrease in circulating VEGF was detected in a study with bevacizumab in rectal cancer, VEGF-A levels may be modulated by cediranib. *(44)* There is a wide inter-individual variation in VEGF-A levels, and an understanding of the factors influencing basal levels of VEGF-A may aid the interpretation of results. Polymorphisms in the VEGF-A gene have been shown to affect expression levels of the protein both in vitro and in vivo. *(45-47)*

Analysis of the HIF1α gene should be included in studies where microvessel density (MVD) is being analyzed as a biomarker. Hypoxia inducible factor 1 (HIFα/ARNT) is a key regulator of cellular response to hypoxia and is thought to play an important role in tumor progression and metastasis through activation of genes that are involved in the regulation of angiogenesis, energy metabolism and other functions. *(48)* Tanimoto et al. have demonstrated a correlation between two polymorphic variants of HIFα and MVD in head and neck cancer. *(49)*

The development of hypertension has been reported in ~11% of patients treated with bevacizumab plus chemotherapy compared to 2% in patients treated with chemotherapy alone, indicating that a proportion of patients on antiangiogenic therapy may be susceptible to the development of hypertension. *(50)* If hypertension is observed in patients treated with cediranib, analysis of candidate genes such as endothelial nitric oxide synthase gene (eNOS) could be undertaken. Variants of eNOS have been associated with essential hypertension and renal disease and may correlate with the development of hypertension in patients treated with antiangiogenic therapy. *(51)* Nitric oxide release is mediated via the activation of kdr/flk-1 through downstream signaling mechanisms, and components of these pathways could provide additional candidates. *(52)*

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below

Ethnic Category	Females	Males	Total
Hispanic or Latino	1	2	3
Not Hispanic or Latino	58	55	113
Ethnic Category: Total of all subjects	59	57	116
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	2	3
Black or African American	6	7	13
Native Hawaiian or other Pacific Islander	0	0	0
White	52	48	100
Racial Category: Total of all Subjects*	59	57	116

3.0 DRUG INFORMATION

3.1 Cediranib (RecentinTM, AZD2171) (NSC 732208) (CTEP IND #72,740)/Placebo

a. DESCRIPTION

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

Other Names: AZD2171 maleate, Recentin™, AZD171

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

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

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

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

Mode of Action: *A*ZD2171 is a highly potent inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase activity, which may inhibit vascular endothelial growth factor-A (VEGF) driven angiogenesis and, as a consequence, constrain solid tumor growth.

b. TOXICOLOGY

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

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1,243 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 2.13, September 29, 2016[1]

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 4.0 Term) [n= 1243]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
ENDOCRINE DISORDERS			
	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)***
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	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)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotrans-ferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Investigations - Other (increased thyroid stimulating hormone)		***Investigations - Other (increased thyroid stimulating hormone) (Gr 2)***
	Lymphocyte count decreased		
	Neutrophil count decreased		

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 4.0 Term) [n= 1243]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INVESTIGATIONS (contd.)			
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 4)***
		Vascular disorders - Other (arterial thrombosis)	
	Vascular disorders - Other (hemorrhage)[2]		

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 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.
3 Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

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 - Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (premature ventricular complexes); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Heart failure; 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
ENDOCRINE DISORDERS - Hyperthyroidism
EYE DISORDERS - Blurred vision; Eye disorders - Other (blindness); Eye disorders - Other (visual disturbance); Papilledema; Photophobia; Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Bloating; Colitis; Colonic perforation; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Flatulence; Gastric necrosis; Gastric perforation; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (hydrops); Gastrointestinal disorders - Other (tongue sensitivity); Ileal perforation; Ileus; Oral cavity fistula; Oral pain; Pancreatitis; 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 failure; Hepatic pain; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice cholestatic)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis
INFECTIONS AND INFESTATIONS - Infection[3]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture; Injury, poisoning and procedural complications - Other (tracheostomy malfunction); Intestinal stoma leak; Venous injury; Wound complication; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin 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 (elevated LDH); 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; Generalized muscle weakness; Muscle weakness left-sided; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (muscle cramps); Musculoskeletal and connective tissue disorder - Other (rotator cuff injury); Myalgia; Myositis; Neck pain; Pain in extremity
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; Dysgeusia; Dysphasia; Encephalopathy; Hydrocephalus; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (coma); Nervous system disorders - Other (right hemiparesis); Nervous system disorders - Other (spinal cord compression); Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Sinus pain; Somnolence; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Confusion; Delirium; Depression; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Cystitis noninfective; Hematuria; Renal and urinary disorders - Other (nephrotic syndrome); 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
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.

Precautions: Hypertension is an expected adverse event with agents that inhibit VEGF signaling. In cediranib (AZD2171) studies, increases in blood pressure have been observed and cases of hypertension have been reported, including CTC grade 4 hypertension and end-organ damage related to hypertension. Clinical experience with cediranib (AZD2171) has shown that hypertension occurs at doses of 20 mg and higher. Cediranib (AZD2171) studies include monitoring of blood pressure and renal function, and a hypertension monitoring and management protocol has been developed which will be appended to all future study protocols.

c. PHARMACOLOGY

How Supplied: For this study, “AZD2171” and matched “Placebo” will be supplied as round, beige, film-coated tablets for oral administration. The 30 mg tablets (and matched placebo) are 9 mm in diameter, the 20 mg tablets (and matched placebo) are 8mm in diameter, and the 15 mg tablets (and matched placebo) are 7 mm in diameter. Each tamper-evident, child-resistant, 75 mL, square, white, opaque, high-density

polyethylene (HDPE) bottle contains 35 tablets.

For “AZD2171”, each tablet contains either 15 mg, 20 mg, or 30 mg of cediranib maleate with mannitol, dibasic calcium phosphate anhydrous, sodium starch glycollate, microcrystalline cellulose, and magnesium stearate. For the matched “Placebo”, each tablet contains mannitol, dibasic calcium phosphate anhydrous, sodium starch glycollate, microcrystalline cellulose, and magnesium stearate. For “AZD2171” and “Placebo”, the film coat consists of hypromellose 2910, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide.

Storage: AZD2171 is shipped at room temperature by U.S. Priority Mail. On arrival, intact bottles should be stored at controlled room temperature [20° to 25°C (68 to 77°F)] and protected from light.

Stability: Shelf-life studies of AZD2171 are continuing and investigators will be notified when lots have expired.

Route of Administration: Oral. AZD2171 tablets should be taken either 1 hour before or 2 hours after meals.

d. SUPPLIER

Investigators with an affiliation with SWOG may request an Investigator’s Brochure by emailing the Pharmaceutical Management Branch’s IB Coordinator at <ibcoordinator@mail.nih.gov> and providing the following:

- the investigator’s full name (first, middle, last)
- the investigator’s NCI investigator number
- the agent name (i.e., “cediranib”)

- the NSC (i.e., “732208”)
- the protocol (i.e., “**S0905**”)
- the requestor’s name, email address, and phone number

Clinical Supplies: Cediranib (NSC 732208/CTEP IND #72,740) and, for Phase II, matching Placebo will be provided free of charge by AstraZeneca Pharmaceuticals and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Phase I (Open Label, Patient-Specific Clinical Supplies)

Cediranib will be supplied in bottles containing 35–30 mg tablets (Cediranib 30 mg) with a child-resistant cap and a tamper-evident seal. In addition, to support dose reductions, Cediranib will also be supplied in bottles containing 35–20 mg tablets (Cediranib 20 mg) and in bottles containing 35– 15 mg tablets (Cediranib 15 mg). Each open label, patient-specific bottle will be laeled with:

- the protocol number (i.e., “**S0905**”)
- the bottle number (i.e., “Bottle 1 of 2” and “Bottle 2 of 2”)
- the number of tablets (i.e., “35 tablets”)
- the patient ID number (e.g., “999999", where “999999” represents a unique patient identifier assigned by SWOG at registration)
- the patient initials (i.e., last initial, first initial, middle initial [e.g., “LFM”])
- the agent identification (i.e., “Cediranib 30 mg” OR “Cediranib 20 mg” OR “Cediranib 15 mg”)
- a blank line for the pharmacist to enter the patient’s name
- administration instructions (i.e., “Take 1 tablet once daily.”)
- storage instructions (i.e., “Store at room temperature (20ºC to 25ºC; 66ºF to 77ºF) and protect from light.”)
- emergency contact instructions
- a Julian date

Phase II (Blinded, Patient Specific Clinical Supplies

Cediranib and matching Placebo will be supplied in bottles containing 35–20 mg tablets (Cediranib 20 mg) or 35–0 mg tablets (Placebo for Cediranib 20 mg) with a child-resistant cap and a tamper-evident seal. In addition, to support dose reductions, Cediranib and matching Placebo will also be supplied in bottles containing 35–15 mg tablets (Cediranib 15 mg) or 35 – 0 mg tablets (Placebo for Cediranib 15 mg). Each blinded, patient-specific bottle will be labeled with:

- the protocol number (i.e., “**S0905**”)
- the bottle number (i.e., “Bottle 1 of 2” and “Bottle 2 of 2”)
- the number of tablets (i.e., “35 tablets”)
- the patient ID number (e.g., “999999", where “999999” represents a unique patient identifier assigned by SWOG at registration)
- the patient initials (i.e., last initial, first initial, middle initial [e.g., “LFM”])
- the agent identification (i.e., “Cediranib 20mg or Placebo” OR “Cediranib 15mg or Placebo”)
- a blank line for the pharmacist to enter the patient’s name
- administration instructions (i.e., “Take 1 tablet once daily.”)
- storage instructions (i.e., “Store at room temperature (20ºC to 25ºC; 66ºF to 77ºF) and protect from light.”)
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2010 = 10, 2011 = 11) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2010 would have a Julian date of '10001' and a bottle labeled and shipped on December 31, 2011 would have a Julian date of '11365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both cediranib and placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496-5725 Monday through Friday between 8:30am and 4:30pm Eastern Time or by emailing <PMBAfterHours@mail.nih.gov> anytime.

Drug Orders: **No open label OR blinded starter supplies will be available for this study.** Open label (Phase I) or blinded (Phase II) patient-specific clinical supplies will be sent to the registering investigator at the time of registration and should arrive within approximately 7 to 10 days. Patients will be registered by the SWOG Statistical Center in Seattle, WA. The assigned patient ID number must be recorded by the registering institution at the time of registration for proper clinical supply dispersion. Once a patient has been registered, the SWOG Statistical Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the SWOG Statistical Center the day the patient is registered and will be processed by PMB the next business day and shipped the following business day. Shipments within the United States will be sent by US Priority Mail (generally two to three day delivery) and shipments to Canada will be sent by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, SWOG would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States clinical sites could expect to receive their order approximately Friday or Monday (depending on the US Mail service) and Canadian clinical sites could expect to receive their order either Thursday or Friday. Shipments to United States clinical sites can be expedited (i.e., receipt on Thursday in the example above) by indicating either UPS or Federal Express and providing the account number to the SWOG Statistical Center at the time the patient is randomized. NOTE: An account number is not needed for regular (U.S. Priority Mail) shipments

Alternatively, active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

S0905 Shipment Schedule

Patient Randomized with SWOG	Initial e-Order Transmitted by SWOG	Initial e-Order Received and Approved by PMB	Initial Order Shipped By PMB	Initial Order Received at Site
Monday	Monday	Tuesday	Wednesday	*
Tuesday	Tuesday	Wednesday	Thursday	*
Wednesday	Wednesday	Thursday	Friday	*
Thursday	Thursday	Friday	Monday	*
Friday	Friday	Monday	Tuesday	*

* Dependent on shipment mechanism. See Section 3.1d/Drug Orders for additional information.

Phase I (Open Label, Patient-Specific Clinical Supplies)

The initial request will be for **2 – 35 tablet bottles** of Cediranib **30 mg** (a **3-cycle / 9-week supply** at a dose of one – 30 mg tablet once daily). Six weeks after the initial electronic request (i.e., three weeks before needed), sites may reorder an additional **2 – 35 tablet bottles** of Cediranib **30 mg** (a **3–cycle / 9-week supply** at a dose of one – 30 mg tablet once daily) by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov). The protocol number (i.e., **S0905**), the assigned patient ID number (e.g., "999999"), the patient initials (e.g., "LFM"), and the number of bottles remaining from the previous shipment must be recorded on each order.

Special Ordering Procedures for Patients Requiring a Dose Reduction.

If the patient is **dose reduced** from cediranib **30 mg** once daily TO cediranib **20 mg** once daily (see Section 8.3), an NCI Clinical Drug Request form must be completed (see above) and faxed to PMB to obtain the cediranib 20 mg tablets. Be sure to specify "Cediranib 20 mg" in the "Strength" field. **Please indicate the cycle and the day of therapy (e.g., Cycle 2, Day 1) of the dose reduction in the comments field.**

If the patient is **dose reduced** from cediranib **20 mg** once daily TO cediranib **15 mg** once daily (see Section 8.3), an NCI Clinical Drug Request form must be completed (see above) and faxed to PMB to obtain the cediranib 15 mg tablets. Be sure to specify "Cediranib 15 mg" in the "Strength" field. **Please indicate the cycle and the day of therapy (e.g., Cycle 2, Day 1) of the dose reduction in the comments field.**

Phase II (Blinded, Patient-Specific Clinical Supplies)

The initial request will be for **2 – 35 tablet bottles** of Cediranib **20 mg** or matched placebo (a **3-cycle / 9-week supply** at a dose of one – 20 mg tablet once daily). Six weeks after the initial electronic request (i.e., three weeks before needed), sites may reorder an additional **2 – 35 tablet bottles** of Cediranib **20 mg** or matched placebo (a **3–cycle / 9-week supply** at a dose of one – 20 mg tablet once daily) by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov). The protocol number (i.e., **S0905**), the assigned patient ID number (e.g., "999999"), the patient initials (e.g., "LFM"), and the number of bottles remaining from the previous shipment must be recorded on each order.

Special Ordering Procedures for Patients Requiring a Dose Reduction.

If the patient is **dose reduced** from cediranib **20 mg** once daily TO cediranib **15 mg** once daily (see Section 8.3), an NCI Clinical Drug Request form must be completed (see above) and faxed to PMB to obtain the cediranib 15 mg tablets. Be sure to specify "Cediranib 15 mg / Placebo" in the "Strength" field. **Please indicate the cycle and the day of therapy (e.g., Cycle 2, Day 1) of the dose reduction in the comments field.**

All drug orders will be shipped directly to the registering physician at the shipping address provided on their current Supplemental Investigator Data Form (IDF) on file with CTEP. The registering investigator must maintain an active investigator registration status with CTEP, DCTD through the annual submission of an FDA Form 1572 (Statement of Investigator), a Curriculum Vitae, a Supplemental Investigator Data Form (IDF), and a Financial Disclosure Form (FDF).

Drug Transfers: Bottles may **NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the registering investigator for a given patient changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-480-4612) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "999999") and the patient initials (e.g., "LFM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "**S0905**"). The julian date/order number (e.g., 10001-9999) should be entered in the "Lot Number" field.

Drug Returns: **Only undispensed clinical supplies should be returned to the PMB**. When it is necessary to return study drug (e.g., sealed bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "999999"), the patient initials (e.g., "LFM"), and the julian date/order number (e.g., 10001-9999) should be entered in the "Lot Number" field. A separate line item is required for each patient ID (e.g., "999999") and for each strength (e.g., "30 mg", "20 mg", "15 mg") being returned. **Dispensed bottles with remaining tablets should be documented in the patient-specific NCI Investigational Agent Accountability Record (i.e., logged is as "returned by patient" and logged out as "destroyed on site") and destroyed on site in accordance with institutional policy**.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov). A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "999999") and for each strength (e.g., "30 mg", "20 mg", "15 mg") on this protocol. The combination julian date/order number in the upper right hand corner of the patient-specific bottle label (e.g., 10001-9999) should be recorded as the lot number.

Emergency Unblinding: In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the **Washington Poison Center (WPC) at 206-526-2121** (see Appendix 18.6). This service is available 24 hours a day, 365 days a year. The WPC will require the protocol number (i.e., "**S0905**"), the patient ID number (e.g., "999999"), and the patient initials (e.g., "LFM") to unblind the patient. Please note that, if a patient is emergently unblinded, he/she is considered to be off-therapy and must discontinue protocol treatment.

Compliance: Patients will be required to return all bottles of study medication at the end of each cycle. The number of tablets remaining should be documented and recorded on the Intake Calendar (see Appendix 18.3).

3.2 Cisplatin (CDDP) (Platinol®) (NSC-119875)

b. DESCRIPTION

Cis-diamminedichloroplatinum (Platinol® or cisplatin) is a heavy metal complex and is water soluble. It is a white lyophilized powder with a molecular weight of 300.1.

Mechanism of Action: It acts as a bifunctional alkylating agent.

b. TOXICOLOGY

Human Toxicology: Human toxicity includes anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, serum uric acid and impairment of endogenous creatinine clearance, as well as renal tubular damage), ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus), peripheral neuropathy and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Raynaud's phenomena and digital ischemia has been described. Anaphylactic-like reactions including facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of administration. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Alopecia, malaise and asthenia have been reported. Rare complications are alopecia, seizures, loss of taste and allergic reactions. Tetany may occur due to hypomagnesemia and/or hypocalcemia. Other electrolyte disturbances may occur. At high doses patients have experienced optic neuritis, □emetrexed□, cerebral blindness, blurred vision, and altered color perception. Patients have also experienced cardiac abnormalities, elevated SGOT and rash. Subsequent courses should not be given until serum creatinine returns to normal if elevated. Audiometric analyses should be monitored and courses withheld until auditory acuity is within normal limits. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

Pregnancy and Lactation: Cisplatin can cause fetal harm when administered to a pregnant woman. In mice, cisplatin is teratogenic and embryotoxic. This drug has been found to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, patients receiving cisplatin should not breast feed.

c. PHARMACOLOGY

Kinetics: After a single IV dose, increased concentration is found in the liver, kidneys and small and large intestines. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding which exceeds 90% of the radioactivity in the second phase. Urinary excretion is incomplete with only 27 to 43% of the radioactivity excreted in the first five days. The initial fractions of radioactivity are largely unchanged drugs. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents. Cisplatin penetrates into CNS poorly.

Formulation: Cisplatin is available as 10 mg and 50 mg vials of dry powder which are reconstituted with 10 ml and 50 ml of Sterile Water for Injection USP, respectively. Cisplatin is also available as an aqueous solution, 1 mg/ml, in 50 or 100 ml vials.

Storage and Stability: The intact vials may be stored at room temperature (15–25°C) for the lot life indicated on the package. Do not refrigerate. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. The reconstituted solution is stable for 20 hours at room temperature, although, due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5-1/2NS (precipitate occurs in D5W).

If cisplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

Administration: In this protocol, cisplatin will be given immediately after preparation as an intravenous infusion over a 2 hour period. **Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin (Platinol) should not be used for preparation or administration, as a black precipitate is formed within 30 minutes.**

d. SUPPLIER

Cisplatin is commercially available, and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

3.3 Pemetrexed for injection (Alimta®) (NSC-698037)

b. DESCRIPTION

Pemetrexed for injection is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is a white to almost-white solid with a molecular formula of C20H19N5Na2O6•7H2O and a molecular weight of 597.49.

c. TOXICOLOGY

The following toxicities occurred in > 10% of patients:

Cardiovascular: Chest paint (38 to 40%); edema (19%)

Central nervous system: Fatigue (80 to 87%); fever (17 to 26%); depression (11 to 14%)

Dermatologic: Rash (17 to 22%); alopecia (11%)

Gastrointestinal: Nausea (39 to 84%; grade 3-4 in 12%); vomiting (25 to 58%; Grade 3-4 in 11%); constipation (30 to 44%); anorexia (35 to 62%); stomatitis/pharyngitis (20 to 28%); diarrhea (21 to 26%)

Hematologic: Neutropenia (11 to 58%); leucopenia (13 to 55%); anemia (33%); thrombocytopenia (9 to 27%). Nadir: 8-10 days, Recovery: 12-17 days.

Neuromuscular and skeletal: Neuropathy (17 to 29%); myalgia (13%)

Renal: Creatinine increased (3 to 16%)

Respiratory: Dyspnea (66%)

Miscellaneous: Infection (17 to 23%

The following toxicities occurred in 1% to 10% of patients:

Cardiovascular: Thrombosis/embolism (4 to 7%); cardiac ischemia (3%)

Endocrine and metabolic: Dehydration (3 to 7%)

Gastrointestinal: Dysphagia/esophagitis/odynophagia (5 to 6%)

Renal: Renal failure (< 1 to 2%)

Miscellaneous: Allergic reaction (2 to 8%)

Neuromuscular and skeletal: Arthralgia (8%)

Drug Interactions: Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of emetrexed. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of emetrexed. Although ibuprofen (400 mg qid) can be administered with emetrexed in patients with normal renal function (creatinine clearance ≥ 80 mL/min), caution should be used when administering ibuprofen concurrently with emetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of emetrexed. In the absence of data regarding potential interaction between emetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following emetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

Decreased Renal Function: Pemetrexed is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance ≥ 45 mL/min. Insufficient numbers of patients have been studied with creatinine clearance < 45 mL/min to give a dose recommendation. Therefore, emetrexed should not be administered to patients whose creatinine clearance is < 45 mL/min.

Pregnancy Category D: Pemetrexed may cause fetal harm when administered to a pregnant woman. Pemetrexed was fetotoxic and teratogenic in mice at i.p. doses of 0.2 mg/kg (0.6 mg/m^2) or 5 mg/kg (15 mg/m^2) when given on gestation days 6 through 15. Pemetrexed caused fetal malformations (incomplete ossification of talus and skull bone) at 0.2 mg/kg (about 1/833 the recommended i.v. human dose on a mg/m^2 basis), and cleft palate at 5 mg/kg (about 1/33 the recommended i.v. human dose on a mg/m^2 basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced litter sizes. There are no studies of emetrexed in pregnant women. Patients should be advised to avoid becoming pregnant. If emetrexed is used during pregnancy, or if the patient becomes pregnant while taking emetrexed, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers: It is not known whether emetrexed or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from emetrexed, it is recommended that nursing be discontinued if the mother is treated with emetrexed.

d. PHARMACOLOGY

Kinetics: The pharmacokinetics of emetrexed administered as a single agent in doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. The total systemic clearance of emetrexed is 91.8 mL/min and the elimination half-life of emetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). The clearance decreases, and exposure (AUC) increases, as renal function decreases. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (Cmax) increase proportionally with dose. The pharmacokinetics of emetrexed do not change over multiple treatment cycles. Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that emetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

Formulation: Pemetrexed is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 500-mg vial contains emetrexed disodium equivalent to 500 mg emetrexed and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

Storage and Stability: Pemetrexed for injection should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Chemical and physical stability of reconstituted and infusion solutions of emetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F), or at 25°C (77°F),

excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. When prepared as directed, reconstituted and infusion solutions of emetrexed contain no antimicrobial preservatives. Discard unused portion. Pemetrexed is not light sensitive.

Administration:

1. Use aseptic technique during the reconstitution and further dilution of emetrexed for intravenous infusion administration.

2. Calculate the dose and the number of emetrexed vials needed. Each vial contains 500 mg of emetrexed. The vial contains an excess of emetrexed to facilitate delivery of label amount.

3. Reconstitute 500-mg vials with 20 mL of 0.9% Sodium Chloride Injection (preservative free) to give a solution containing 25 mg/mL emetrexed. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted emetrexed solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.

4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is observed, do not administer.

5. The appropriate volume of reconstituted emetrexed solution should be further diluted to 100 mL with 0.9% Sodium Chloride Injection (preservative free) and administered as an intravenous infusion over 10 minutes.

6. Chemical and physical stability of reconstituted and infusion solutions of emetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or ambient room temperature (see USP Controlled Room Temperature) and lighting. When prepared as directed, reconstitution and infusion solutions of emetrexed contain no antimicrobial preservatives. Discard any unused portion.

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Co-administration of emetrexed with other drugs and diluents has not been studied, and therefore is not recommended.

d. SUPPLIER

Pemetrexed is commercially available and should be purchased by a third party. Pemetrexed will not be supplied by the NCI.

Please refer to the Physician's Desk Reference and package insert for complete information.

4.0 STAGING CRITERIA

Staging criteria are not applicable to this protocol.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S0905** Prestudy Form (Form #39381) and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 Disease Related Criteria

_____ a. Patient must have histologically or cytologically confirmed diagnosis of malignant pleural mesothelioma. Surgical resection must not be planned.

_____ b. Patients must have measurable or non-measurable disease by both RECIST (see Section 10.1) and modified RECIST criteria for pleural tumors (see Section 10.5) as documented by CT scan. Examinations for assessment of measurable disease must have been completed within 28 days prior to registration. Examinations for assessment of non-measurable disease must have been performed within 42 days prior to registration. All disease must be assessed and documented on the RECIST 1.1 and Modified RECIST Baseline Tumor Assessment Form (Form #35990).

_____ c. Patients must not have received any prior systemic therapy (chemotherapy or other biologic therapy) for their unresectable malignant pleural mesothelioma. Prior systemic chemotherapy or biologic therapy is allowed as neoadjuvant or adjuvant treatment, disease has now recurred, and all systemic treatment was completed > 6 months prior registration. Prior therapy must not have included cediranib.

_____ d. Patients may have received prior surgery (e.g., pleurectomy, pleurodeisis) provided at least 28 days have elapsed since surgery (thoracic or other major surgeries) and patients have recovered from all associated toxicities at the time of registration. There must be no anticipated need for major surgical procedures during protocol treatment.

5.2 Prior Therapy Criteria

_____ e. Patients may have received prior radiation therapy provided at least 28 days have elapsed since the last treatment and patients have recovered from all associated toxicities at the time of registration.

_____ f. Institutions must seek additional patient consent for the banking and future use of specimens as described in Section 15.3.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.3 Clinical/Laboratory Criteria

_____ g. Patient must have Zubrod performance status 0-2 (see Section 10.4).

_____ h. Patient must have adequate bone marrow function as evidenced by all of the following: absolute neutrophil count ≥ 1,500 mcl; platelets ≥ 100,000/ml; hemoglobin ≥ 9.0 g/dl (may be reached by transfusion). These results must have been obtained within 28 days prior to registration.

_____ i. Patient must have adequate hepatic function as defined by total bilirubin ≤ 1.5 x Institutional Upper Limit of Normal (IULN) and SGOT or SGPT ≤ 2.5 x IULN (if liver metastases are present, SGOT or SGPT must be ≤ 5.0 x IULN). These results must be obtained within 28 days prior to registration.

_____ j. Patient must have adequate renal function as evidenced by BOTH of the following:

- Serum creatinine ≤ 1.5 x IULN. Must be obtained within 28 days prior to registration.
- Calculated creatinine clearance ≥ 60 mL/min. Creatinine level (mg/dl) used in calculation must be obtained within 28 days prior to registration.

Calculated creatinine clearance = $\frac{(140\text{-age}) \times \text{weight (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$

_____ k. Urine protein must be screened by urine analysis within 28 days prior to registration. Patient must not have greater than +1 proteinuria on two consecutive dipsticks taken no less than 7 days apart. However, if the first urinalysis shows no protein, then a repeat urinalysis is not required.

_____ l. Patient must have an ECG performed within 42 days prior to registration. Patient must not have mean QTc > 500 msec (with Bazett's correction) in screening electrocardiogram, or other significant ECG abnormality, NYHA classification III or IV (see Appendix 18.5). Patient must not require concurrent use of drugs or biologics with proarrhythmic potential (see Appendix 18.4 for list of agents).

_____ m. Patient must not be receiving any medication that may markedly affect renal function (e.g., vancomycin, amphotericin, pentamidine).

_____ n. Patient must not have had clinically significant hemoptysis, defined as greater than 1 tablespoon of bright red blood, within one year prior to registration. Although hemoptysis has not been associated with cediranib, it may be a class effect for anti-angiogenic agents and therefore a risk factor for this experimental agent.

_____ o. Patient must be able to swallow oral medications.

_____ p. Patients must not have known HIV infection because their immune system may not tolerate the investigational treatment and because antiretroviral treatment may interact with the study agents.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ q. Patients must not be pregnant or nursing because of increased risk of harm to a nursing infant or fetus including fetal death from the chemotherapeutic and biologic agents. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

_____ r. Patient must have no plans to receive concurrent chemotherapy, hormonal therapy, radiotherapy, immunotherapy or any other type of therapy for treatment of cancer while on this protocol treatment.

_____ s. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

5.4 Regulatory Criteria

_____ t. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ u. As a part of the OPEN registration process (see Section 13.2 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

For the Phase II portion of the trial, patients will be randomized using a dynamic balancing algorithm with stratification based on *(53)*:

6.1 Performance status: 0 or 1 versus 2

6.2 Histologic subtype: epitheliod versus biphasic/sarcomatoid

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Tsao at 713/792-6363 or Dr. Vogelzang at 702/952-3452. For dosing principles or questions, please consult the Southwest Oncology Group Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Good Medical Practice

The following tests (and/or assessments) are recommended within 28 days prior to registration in accordance with Good Medical Practice. Results of these tests do not determine eligibility and minor deviations from normal limits would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. **If there are significant deviations in these tests/assessments that could impact patient safety, it is highly recommended that the registering investigator discuss the patient with the Study Coordinator prior to registering.**

a. Uric acid

b. Serum mesothelin-related peptide

c. Patients at an increased risk for compromised left ventricular ejection fraction (LVEF) should have a baseline ECHO/MUGA and troponins to help identify compromised LVEF should it occur. Investigators should consider patients who have the following risk factors at an increased risk for compromised LVEF:

1. New York Heart Association classification of II (see Appendix 18.5)

2. Prior central thoracic radiation therapy (RT), including RT to the heart

3. History of myocardial infarction within 12 months

d. Any non-required baseline test result ≥ Grade 3 should be noted in the patient's medical record as an abnormality with an indication that the treating investigator feels it is safe for the patient to enroll on the study.

e. Performance of an audiogram is recommended to document baseline hearing loss status in the event of possible hearing loss due to cisplatin administration. Patients with significant clinical hearing loss should be willing to accept the potential for worsening of symptoms.

f. Patient should not have resting blood pressure > 150/90 in the presence or absence of anti-hypertensive therapy.

g. Patient should not have symptomatic congestive heart failure resulting in a resting O_2 saturation of < 92% on room air. Patient should not have unstable angina pectoris. Patient should not have cardiac arrhythmia requiring maintenance medication. Patient should not require oxygen at rest. Patients with hypoxia from mesothelioma disease and not from congestive heart failure are allowed on the trial.

h. Patients should have chemistry tests including serum chemistry for potassium, magnesium, albumin, electrolytes (sodium, chloride, bicarbonate), glucose, calcium, LDH, phosphorus, total protein, alkaline, phosphatase, and BUN. Results should be within normal limits. These should be obtained within 28 days prior to registration.

i. Patients should have a thyroid function test (TSH, free T4) with results within normal limits within 28 days prior to registration.

j. Patient should not have suffered an arterial thromboembolic event within the previous 1 year. Although arterial thrombotic events have not been associated with cediranib, it may be a class effect for anti-angiogenic agents and therefore a risk factor for this experimental agent.

k. Patient should not have > Grade 2 neuropathy.

l. Patient should not have chronic diarrhea ≥ Grade 1.

m. Patient should not have ongoing or active infection requiring parenteral therapy at the time of registration.

n. Patients on anticoagulants should have INR performed.

7.2 Treatment Overview

The study will be conducted in two sequential parts. A patient may be enrolled to either the Phase I portion or the Phase II portion, but not both.

Phase I – Details are in Section 7.4.

Phase II – Details are in Section 7.5.

7.3 Pre-Medication

Pre-Medication – applicable to both the Phase I and Phase II portions of the study

Pre-medication for pemetrexed and cisplatin is **required** as detailed below.

Agent	Dose	Route	Schedule
Folic Acid	400-1,000 mcg or equivalent [a]	PO	Daily; beginning 7 days before first dose of pemetrexed and continuing until 3 weeks after the last dose of pemetrexed
Vitamin B12	1,000 mcg	IM	q 9 weeks; beginning 7 days before first dose of pemetrexed and continuing until 3 weeks after the last dose of pemetrexed [b]
Dexamethasone	4 mg [c]	PO twice per day (or as 8 mg every morning)	Day before, day of, and day after all doses of pemetrexed unless clinically contraindicated
Aprepitant [d]	125 mg	PO	One hour before each cisplatin dose
Aprepitant [d]	80 mg	PO	Daily on Days 2, 3, 4 of each cycle
Ondansetron [d]	8 mg	IVPB in 50 mL NS	Day 1 of each cycle
Ondansetron [d]	8 mg	PO	Daily on Days 2, 3, 4 of each cycle

[a] An acceptable range of folic acid intake is given above. If patient is already on vitamin supplement that includes 400-600 mcg folic acid daily, this is acceptable and no additional folic acid needs to be taken.

[b] i.e., if a scheduled vitamin B12 dose falls within 3 weeks following pemetrexed, it should be given.

[c] Higher or additional doses are permitted for reasons other than routine rash prophylaxis (e.g., antiemetic prophylaxis)

[d] Or acceptable alternative

c. Phase I Portion of the Study

NOTE: No open label starter supplies will be available for this study. Initial open label, patient-specific clinical supplies of cediranib will be shipped from the Pharmaceutical Management Branch (PMB) to the registering investigator at the time of patient registration and should arrive within 7 to 10 days (see Section 3.1).

Agent*	Dose	Route	Schedule*
Pemetrexed	500 mg/m^2	IV over 10 minutes	Day 1 of each cycle, for 6 cycles only
Cisplatin	75 mg/m^2	in 1 L NS IVPB with 25 grams mannitol over 2 hours	Day 1 of each cycle, for 6 cycles only
Cediranib	Cohort 1 (Dose Level 0): 30 mg Cohort 2 (Dose Level -1): 20 mg	PO	Daily until meeting one of the criteria in Section 7.10**

* Each cycle is 21 days long.

** Cediranib should be taken either one hour before or two hours after eating.

IMPORTANT NOTE: The Phase I portion of this trial is now closed. Rapid reporting of dose-limiting toxicities (Section 15.1) is no longer required.

a. Dose Determination Rules

1. Dose Limiting Toxicity (DLT) is defined in Section 7.4b.

2. Only DLTs occurring during Cycle 1 will be used to guide dosing determination of cediranib.

3. Patients will be considered evaluable for DLT if they received at least 14 doses of cediranib at the assigned dose during Cycle 1 and at least one dose each of emetrexed and cisplatin, or if they developed a DLT. If a patient does not develop a DLT but does not complete at least 14 doses of cediranib and one dose each of emetrexed and cisplatin during Cycle 1 due to any reason, the patient will be considered not evaluable for DLT and will be replaced.

b. The following dosing scheme will be used for dose determination:

Cohort 1:
Evaluate up to 10 patients at Dose Level 0 (30 mg daily):

- Enroll 6 patients, evaluate for toxicity, enroll additional patients as required
- If 3 or more of the initial 6 patients have DLT at Dose Level 0 stop enrollment at this dose and continue to Dose Level -1.
- If in initial 6 patients, 2 or fewer patients have DLT at Dose Level 0 enroll 4 additional patients.
- If 3/10 or fewer patients have DLT this will be the MTD for the Phase II trial.
- If more than 3/10 patients have DLT at Dose Level 0 stop enrollment at this dose after the 4th patient with DLT and continue to Dose Level -1.

Cohort 2:
If Dose Level 0 is not the MTD, evaluate up to 10 patients at Dose Level -1 (20 mg daily):

- Enroll 6 patients, evaluate for toxicity, enroll additional patients as required
- If 3 or more of the initial 6 patients have DLT at Dose Level -1 stop enrollment at this dose and conclude neither dose is the MTD. Further testing will need to be discussed.
- If in initial 6 patients, 2 or fewer patients have DLT at Dose Level -1 enroll 4 additional patients,
- If 3/10 or fewer patients have DLT this will be the dose for the Phase II trial.
- If more than 3/10 patients have DLT at Dose Level -1 stop enrollment at this dose after the 4th patient with DLT and conclude neither dose is the MTD. Further testing will need to be discussed.

c. Definition of Dose-Limiting Toxicity

Toxicities will be graded according to the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events. This can be reviewed at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
Dose-limiting toxicities (DLT) apply only during Cycle 1 and must be drug-related (i.e. possibly, probably or definitely related to one of the 3 study drugs). The following events occurring in the first cycle of treatment are considered dose limiting.

1. Febrile neutropenia

2. Grade 4 neutrophil count decrease for more than 7 days' duration

3. Grade 4 platelet count decrease

4. Grade 3 or 4 non-hematologic toxicity (excluding alopecia)

7.5 Phase II Portion of the Study

NOTE: No blinded starter supplies will be available for this study. Initial blinded, patient-specific clinical supplies of cediranib / placebo will be shipped from the Pharmaceutical Management Branch (PMB) to the registering investigator at the time of patient registration and should arrive within 7 to 10 days (see Section 3.1).

Agent*	Dose	Route	Schedule*
Pemetrexed	500 mg/m^2	IV over 10 minutes	Day 1 of each cycle, for 6 cycles only
Cisplatin	75 mg/m^2	in 1 L NS IVPB with 25 grams mannitol over 2 hours	Day 1 of each cycle, for 6 cycles only
Cediranib or Placebo	20 mg	PO	Daily until meeting one of the criteria in Section 7.10**

* Each cycle is 21 days long.

** Cediranib should be taken either one hour before or two hours after eating.

7.6 Blood Pressure Monitoring

Blood pressure monitoring is required for all patients on this study according to the schedule indicated in Section 9.0.

Patients should have their blood pressure checked at routine visits.

Experience 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. Patients should therefore be encouraged to seek medical advice should they be concerned with any symptoms that may be associated with high blood pressure.

7.7 Drug Compliance

Drug compliance will be recorded by patients in the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.8 General Concomitant Medication and Supportive Care Guidelines

a. Any medication that is considered necessary for the patient's safety and well-being may be given at the discretion of the treating investigator(s).

b. Caution should be exercised in concomitant use of any medication that may significantly affect hepatic CYP450 drug metabolizing activity by way of enzyme induction (e.g. phenytoin) or inhibition (e.g. ketoconazole, ritonavir, erythromycin) within 2 weeks of the first dose of cediranib and throughout the study period. (See Appendix 18.7 for a list of medications.)

c. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Ibuprofen (400 mg qid) can be administered with pemetrexed in patients with normal renal function (creatinine clearance ≥ 80 mL/min), but caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of and 2 days following administration of pemetrexed.

In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of and 5 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal and gastrointestinal toxicity.

NSAIDs with short half-lives include: diclofenac (Volteran), indomethacin (Indocin), tolmetin (Tolectin), meclofenamaic acid (Meclomen), mefenamic acid (Ponstel), fenoprefen (Nalfon), flurbiprofen (Ansaid), ibuprofen (Motrin), ketoproten (Orudis).

NSAIDs with long half-lives include: etodolac (Iodine), ketordac (Toradol), sulindac (Clinoril), naproxen (Naprosyn), naproxen sodium (Anaprox), oxaprozin (Daypro), nabumetone (Relafen), diflunisal (Dolobid), salsalate, celecoxib (Celebrex), rofecoxib (Vioxx), valdecoxib (Bextra), meloxicam (Mobic), piroxicam (Feldene).

d. For elective surgery during the study it is recommended that all protocol treatment be stopped for 2 consecutive weeks prior to the surgical procedure. Treatment can be restarted when the surgical wound has healed. If emergency surgery is performed, precautions should be taken to minimize the potential risk of bleeding and thrombosis associated with this class of agents, all protocol treatment should be stopped and close monitoring for bleeding, wound healing and thromboembolic complications should be initiated. If patients are off protocol treatment for more than 4 weeks due to elective or emergent surgery, they will be removed permanently from protocol treatment.

7.9 CTEP Requirements

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.8, the **S0905** Treatment Form [Form #39146] and the **S0905** Adverse Event Form [Form #19062]). A cycle is defined as 21 days.

7.10 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.2).

b. Unacceptable toxicity.

c. Treatment delay of all 3 drugs for any reason > 2 weeks during the first 6 cycles of concurrent treatment. (EXCEPTION: protocol treatment may be delayed up to 4 weeks for elective or emergent surgery as described in Section 7.8.)

d. Treatment delay for any reason > 2 weeks during maintenance treatment with single agent cediranib/placebo. (EXCEPTION: cediranib/placebo may be delayed up to 4 weeks for elective or emergent surgery as described in Section 7.8.)

e. The patient may withdraw from the study at any time for any reason.

7.11 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice (Form #52393).

7.12 Follow Up Period

All patients will be followed until death or 3 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria

The CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE), will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
All appropriate treatment areas should have access to a copy of the CTEP Active Version of the CTCAE.

8.2 General Considerations

a. If a patient requires a treatment delay of all 3 drugs for any reason > 2 weeks during the first 6 cycles of concurrent treatment, they must be removed from protocol treatment. (EXCEPTION: protocol treatment may be delayed up to 4 weeks for elective or emergent surgery as described in Section 7.8.)

b. If a patient requires a treatment delay for any reason > 2 weeks during maintenance treatment with single agent cediranib/placebo, they must be removed from protocol treatment. (EXCEPTION: cediranib/placebo may be delayed up to 4 weeks for elective or emergent surgery as described in Section 7.8.)

c. There are no dose escalations. If a dose reduction is mandated by toxicity, there will be no dose re-escalation even if toxicity resolves.

d. If multiple toxicities are experienced, dose modification will be based on the toxicity requiring the largest dose reduction.

8.3 Dose levels

NOTE: Please see Section 3.1d ("Special Ordering Procedures for Patients Requiring a Dose Reduction") for instructions on ordering replacement "Cediranib 20 mg" or "Cediranib 15mg" clinical supplies if your patient is dose reduced.

a. Cediranib - Phase I portion of the study

Dose level 0	30 mg
Dose level -1	20 mg
Dose level -2	15 mg
Dose level -3	Permanently remove patient from protocol treatment

b. Cediranib - Phase II portion of the study

The following dose de-escalation schema will be used:

Dose level 0	20 mg
Dose level -1	15 mg
Dose level -2	Permanently remove patient from protocol treatment

c. Cisplatin

Dose level 0	75 mg/m^2
Dose level -1	60 mg/m^2 or change to carboplatin AUC 6
Dose level -2	Carboplatin AUC 5
Dose level -3	Permanently remove patient from protocol treatment

d. Pemetrexed

No dose modifications are allowed for pemetrexed.

8.4 Hematologic toxicities

Grade 1-2

No dose modifications

Grade 3-4

Hold all treatment until toxicities resolve to ≤ Grade 2. If patient experiences Grade 4 myelosuppression and growth factor support was not given, patients should receive growth factor support in all subsequent cycles of therapy (see Section 8.9). If growth factor support was given yet Grade 4 myelosuppression still occurs, then dose -1* should be instituted once the toxicity resolves. Patients should continue to receive growth factor support in all subsequent cycles of therapy. Patients unable to continue cediranib whose symptoms do not resolve within 2 weeks will be permanently removed from cediranib.

*Cediranib/placebo and cisplatin may be modified singly or as a doublet at the investigator's discretion.

8.5 Non-hematologic toxicities

NOTE: This section refers to toxicities other than those listed in Sections 8.6-8.8.

Grade 1-2, or Grade 3 unrelated to chemotherapy

No dose modifications

Grade 3 and related to chemotherapy

Cisplatin and pemetrexed may be held for 1 week to allow for toxicities to resolve. During that time, cediranib will be continued. When the toxicity resolves to ≤ Grade 1, patient's treatment will be resumed at the same dose level. If patient continues to have Grade 2-3 non-hematologic toxicity, a decrease to dose -1* can be made. However, if the toxicity is related to cisplatin induced renal dysfunction or neuropathy or nausea/vomiting, patient may be switched from the cisplatin to carboplatin (AUC 6).

*Cediranib/placebo and cisplatin may be modified singly or as a doublet at the investigator's discretion.

Grade 4

Hold all treatment until toxicities resolve to ≤ Grade 2. Upon resolution resume treatment at dose -1*. Patients unable to continue cediranib whose symptoms do not resolve within 2 weeks will be permanently removed cediranib.

* Cediranib/placebo and cisplatin may be modified singly or as a doublet at the investigator's discretion.

8.6 Proteinuria

Although patients with > 1+ proteinuria at entry are ineligible, increases in proteinuria may occur during treatment and should be managed as follows.

Proteinuria Value	Monitoring	Dose modification
≥ 1+ (dipstick or equivalent routine laboratory analysis)	Perform the following tests: • 24-hour urine collection for total protein and creatinine • microscopic examination of fresh urine • urine protein electrophoresis (at first occurrence of > 1+ proteinuria only)	See below.
Based on results of the 24-hour urine collection:		
< 1g protein (24-hour collection)	Continue dipstick or equivalent routine laboratory analysis	Continue planned dose
≥ 1g but ≤ 2g protein (24-hour collection)	Perform 24-hour urine collection (total protein, creatinine) prior to day 1 of each subsequent cycle of therapy (q4w) until total protein is < 500 mg/24 hours.	Decrease one dose level; continue treatment
> 2 g protein (24-hour collection)	Perform 24-hour urine collection (total protein, creatinine) weekly until proteinuria is < 2g.	Hold cediranib. When protein is < 2g/24 hours, resume treatment at one lower dose level.
	Perform 24-hour urine collection (total protein, creatinine) prior to day 1 of each subsequent cycle of therapy (q4w).	Continue until patient is off protocol treatment.

8.7 Management of Abnormal Thyroid Function Tests

Cediranib therapy has been associated with increases in TSH. In the majority of patients this has not resulted in reductions in either total thyroxine or free T4 to below the lower limit of normal range, but clinical hypothyroidism has been reported in a small number of patients. Patients have responded to replacement therapy without the need for stopping or reducing the dose of cediranib.

Replacement levothyroxine should be given when clinically indicated to normalize the thyroxine level to within the normal range, and before the patient becomes clinically symptomatic. Replacement levothyroxine therapy may also be considered in patients with TSH increases (and thyroxine levels within the normal range), together with adverse events and symptoms suggestive of incipient hypothyroidism. Thyroid function should be monitored frequently and the dose of levothyroxine should be titrated as required.

8.8 Management of Diarrhea

Diarrhea should be treated as an early stage (Grade 1) with loperamide or similar agent. The patient should be given a prescription to take as required at home.

For Grade 3-4 diarrhea refractory to oral and anti-diarrheal medication all treatment will be held. If ≥ Grade 3 diarrhea persists after 2 weeks, both loperamide and study medication should be discontinued. If the toxicity resolves to ≤ Grade 1, then the loperamide will be restarted and the dose reduced, study medication may also be restarted at a reduced dose. If ≥ Grade 3 diarrhea recurs loperamide and study medication should be discontinued.

8.9 Management of Hypertension

Increases in blood pressure 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/placebo treatment has been seen in animal studies as well as clinical trials. Specific guidance for management of this AE is provided below.

When managing mild to moderate hypertension, the following principles must be noted:

- Cediranib may cause rapid increase in BP in some patients.
- Calcium-channel antagonists are the first line agents of choice.
- If calcium channel antagonists are contraindicated, β-blockers are second choice agents.
- Increase nti-hypertensives to maximum doses and add additional agents as required.
- It is recommended that no more than 2 drugs are added in a 48-hour period before temporarily stopping cediranib.

The following cautions and contraindications should be noted:

- Calcium-channel blockers: use with caution in patient with tachyarrhythmia aortic stenosis, unstable angina or congestive cardiac failure and may cause headache.
- Short-acting dihydropyridines should be avoided since they may precipitate abrupt fall in BP and increase of myocardial ischemia, infarction or stroke
- Beta-blockers: contraindicated in patients with asthma, chronic obstructive pulmonary disease and A-V block, they should be used with caution in patients with peripheral vascular disease and glucose intolerance and may cause fatigue.
- If diuretics are to be used, thiazides rather than loop diuretics are recommended.

BP measurements - systolic/diastolic	Interval	Treatment/Dose Modification
Patients **not** receiving maximal antihypertensive therapy:		
≥ 150 mmHg (systolic) **OR** ≥ 90 mmHg (diastolic)	Two BP readings at least 1 hour apart	• Add new or additional antihypertensive meds or increase dose of existing meds • Maintain dose of cediranib
> 200 mmHg (systolic) **OR** > 110 mmHg (diastolic)	Two BP readings during a 1-week period	• Hold cediranib • Monitor patient closely for hypotension (if on antihypertensive meds) until cediranib is restarted. • Resume treatment at same dose level when BP falls to < 150/90.
Patients receiving maximal antihypertensive therapy*:		
> 160 mmHg (systolic) **OR** > 105 mmHg (diastolic)	2 BP readings at least 1 hour apart	• Hold cediranib • Maintain antihypertensive meds and monitor patient closely for hypotension until cediranib is restarted. • Resume treatment at one lower dose level when BP falls to < 150/90
* Maximal antihypertensive therapy is defined as four antihypertensive medications given for 2 weeks.		

Notes:

- While patients are receiving treatment with cediranib, the early initiation of antihypertensive treatment for Grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a Grade 3 adverse event.
- Decisions to hold or decrease the cediranib dose during treatment must be based on BP readings taken in the clinic by a medical professional.

8.10 Guidelines for Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

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

8.11 Guidelines for Patients who develop Compromised Left Ventricular Ejection Fraction (LVEF)

a. Asymptomatic Decrease in LVEF

The decision to continue or hold cediranib/placebo 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:

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

Permanently discontinue all protocol treatment if:

- Two consecutive HOLD categories occur.
- Three intermittent HOLD categories occur (at the discretion of the investigator, cediranib/placebo may also be permanently discontinued prior to the occurrence of 3 intermittent HOLD categories).

IF LVEF is maintained at a "Continue and repeat MUGA/ECHO" or improves from a HOLD to a "Continue and repeat MUGA/ECHO" category, additional MUGA scans/echocardiograms prior to the next scheduled MUGA/ECHO will be at the discretion of the treating investigator.

b. Symptomatic Cardiac Events

Discontinue all protocol treatment if:

- a patient has symptoms of congestive heart failure (CHF) and a diagnosis of CHF is confirmed.
- a patient has a myocardial infarction.

8.12 G-CSF

Prophylactic use of G-CSF for myelosuppression is recommended. However, use of G-CSF is at the discretion of the treating physician. If used, it must be used in accordance with the ASCO guidelines (http://www.jco.org/cgi/content/full/18/20/3558). The use of erythropoietin simulating agents is NOT recommended.

8.13 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Tsao at 713/792-6363 or Dr. Vogelzang at 709/952-3452.

8.14 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Coordinator and NCI via AdEERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 STUDY CALENDAR - Phase I Portion

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			MAINTE-NANCE $ Cycles 7+			& F/U After Off Treatment Prior	√ F/U Afte
REQUIRED STUDIES	PRE	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK		
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	to Prog	Pro
PHYSICAL																								
History and Physical Exam ¢	X	X			X			X			X			X			X			X			X	X
Blood Pressure Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X #	X #
Weight and Performance Status ¢	X	X			X			X			X			X			X			X			X	X
Disease Assessment	X							X						X						X			X	
Baseline Abnormality Assessment	X																							
Toxicity Notation		X%	X%	X%	X			X			X			X			X			X			X #	X #
Review intake calendar ¢		X			X			X			X			X			X			X				
LAB ¢																								
CBC/ Differential/ Platelets	X	X			X			X			X			X			X			X				
Bilirubin	X	X			X			X			X			X			X			X				

Calendar continued on next page.

SGOT or SGPT	X	X			X			X			X			X			X			X			
Serum Creatinine	X	X			X			X			X			X			X			X			
Urine dipstick (protein)	X	X			X			X			X			X			X			X			
ECG £	X				X			X															
Serum Chemistry ¥	X				X			X			X			X			X			X			
TSH, Free T4	X				X			X			X			X			X			X			
Uric acid ¥	X																						
Serum mesothelin-related peptide ¥	X																						
ECHO/MUGA ┼	X							X						X						X			
Troponin T or Troponin I ┼	X							X						X						X			
INR for patients on anticoagulants ¥	X	X			X			X			X			X			X			X			
Audiogram ¥	X																						
SCANS																							
Chest CT ¶	X							X						X						X		X	
CT or MRI of the brain	X																						

Calendar continued on next page.

SPECIMEN SUBMISSION																								
Slides for pathology review (see Section 15.2a)	X																							
Serum, plasma and buffy coat (see Section 15.3a.1) €		X	X	X	X			X			X			X			X			X				
Whole blood (see Section 15.3a.2) €		X																						
Paraffin-embedded tissue (see Section 15.3a.3) €	X																							
TREATMENT																								
Folic Acid	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Vitamin B12	X									X									X					
Dexa-methasone		X			X			X			X			X			X							
Aprepitant		X			X			X			X			X			X							
Ondansetron		X			X			X			X			X			X							
Pemetrexed		X			X			X			X			X			X							
Cisplatin		X			X			X			X			X			X							
Cediranib Δ		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Calendar continued on next page.

NOTE: Forms are found in Section 18.0. Forms submission guidelines may be found in Section 14.0.

¢ Physical exams, weight, performance status and laboratory tests must be done prior to the start of every cycle.

£ Required for all patients at baseline (**see Section 5.12**). Suggested at other time points if clinically indicated.

¥ Results of these tests do not determine eligibility but are recommended prior to registration and during treatment in accordance with Good Medical Practice (see Section 7.1).

┼ Only applicable to patients at increased risk for compromised LVEF (as defined in Section 7.1c). These tests are required prestudy for Good Medical Practice (see Section 7.1 for guidance on timing and interpretation of those test results) and are recommended during treatment where indicated.

¶ Chest CT must be performed prior to the start of every other cycle. If patient is removed from protocol treatment prior to progression, scans must continue every 6 weeks until progression or symptomatic deterioration. Scans must be documented on the Follow-Up Tumor Assessment Form - RECIST 1.1 and Modified RECIST (Form #23757). RESPONSE SHOULD BE CONFIRMED BY A SECOND DETERMINATION AT LEAST 4 WEEKS AFTER A COMPLETE OR PARTIAL RESPONSE HAS BEEN NOTED.

€ If additional consent is granted.

Δ Continuous oral daily dosing (see Section 7.4).

% Dose-limiting toxicities must be reported weekly during Cycle 1 (see Section 15.1).

& If patient is removed from protocol treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating physician) must take place every 6 weeks until progression

√ After disease progression, follow-up will occur (with lab tests performed at the discretion of the treating investigator) every 6 months for the first two years and then at the end of the third year after registration.

Toxicity notation will continue until resolution of any adverse events. Blood pressure monitoring will continue until the resolution of any hypertension.

$ During maintenance therapy, items marked under physical and laboratory should be performed every 6 weeks until patient meets one of the criteria in Section 7.10. Disease assessments and CT scans are to take place every 6 weeks.
NOTE: Blood pressure monitoring must continue at the noted interval (weekly) for safety purposes.

9.2 Phase II Portion

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			MAINTE-NANCE $ Cycles 7+			& F/U After Off Treat Prior to Prog
REQUIRED STUDIES	PRE	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
PHYSICAL																							
History and Physical Exam ¢	X	X			X			X			X			X			X			X			X
Blood Pressure Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X #
Weight and Performance Status ¢	X	X			X			X			X			X			X			X			X
Disease Assessment	X							X						X						X			X
Baseline Abnormality Assessment	X																						
Toxicity Notation		X			X			X			X			X			X			X			X #
Review intake calendar ¢		X			X			X			X			X			X			X			
LABORATORY ¢																							
CBC/Differential/Platelets	X	X			X			X			X			X			X			X			
Bilirubin	X	X			X			X			X			X			X			X			
SGOT or SGPT	X	X			X			X			X			X			X			X			
Serum Creatinine	X	X			X			X			X			X			X			X			
Urine dipstick (protein)	X	X			X			X			X			X			X			X			

Calendar continued on next page.

ECG £	X				X			X														
Serum Chemistry ¥	X				X			X			X			X				X				
TSH, Free T4	X				X			X			X			X				X				
Uric acid ¥	X																					
Serum mesothelin-related peptide ¥	X																					
ECHO/MUGA ┼	X							X						X						X		
Troponin T or Troponin I ┼	X							X						X						X		
INR for patients on anticoagulants ¥	X	X			X			X			X			X				X				
Audiogram ¥	X																					
SCANS																						
Chest CT ¶	X							X						X						X		X
CT or MRI of the brain	X																					
SPECIMEN SUBMISSION																						
Slides for pathology review (see Section 15.2a)	X																					
Serum, plasma and buffy coat (see Section 15.3a.1) €		X	X	X	X			X			X			X				X		X		
Whole blood (see Section 15.3a.2) €		X																				

Calendar continued on next page.

Paraffin-embedded tissue (see Section 15.3a.3) €	X																						
TREATMENT																							
Folic Acid	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Vitamin B12	X									X									X				
Dexamethasone		X			X			X			X			X			X						
Aprepitant		X			X			X			X			X			X						
Ondansetron		X			X			X			X			X			X						
Pemetrexed		X			X			X			X			X			X						
Cisplatin		X			X			X			X			X			X						
Cediranib / Placebo Δ		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Calendar continued on next page.

NOTE: Forms are found in Section 18.0. Forms submission guidelines may be found in Section 14.0.

¢ Physical exams, weight, performance status and laboratory tests must be done prior to the start of every cycle.

£ Required for all patients at baseline (**see Section 5.12**). Suggested at other time points if clinically indicated.

¥ Results of these tests do not determine eligibility but are recommended prior to registration and during treatment in accordance with Good Medical Practice (see Section 7.1**).**

┼ Only applicable to patients at increased risk for compromised LVEF (as defined in Section 7.1c**)**. These tests are required prestudy for Good Medical Practice (see Section 7.1 for guidance on timing and interpretation of those test results) and are recommended during treatment where indicated.

¶ Chest CT must be performed prior to the start of every other cycle. If patient is removed from protocol treatment prior to progression, scans must continue every 6 weeks until progression or symptomatic deterioration. Scans must be documented on the Follow-Up Tumor Assessment Form - RECIST 1.1 and Modified RECIST (Form #23757). RESPONSE SHOULD BE CONFIRMED BY A SECOND DETERMINATION AT LEAST 4 WEEKS AFTER A COMPLETE OR PARTIAL RESPONSE HAS BEEN NOTED.

€ If additional consent is granted.

∆ Continuous oral daily dosing (see Section 7.5).

& If patient is removed from protocol treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating physician) must take place every 6 weeks until progression.

√ After disease progression, follow-up will occur (with lab tests performed at the discretion of the treating investigator) every 6 months for the first two years and then at the end of the third year after registration.

Toxicity notation will continue until resolution of any adverse events. Blood pressure monitoring will continue until the resolution of any hypertension.

$ During maintenance therapy, items marked under physical and laboratory should be performed every 6 weeks until patient meets one of the criteria in Section 7.10. Disease assessments and CT scans are to take place every 6 weeks. NOTE: Blood pressure monitoring must continue at the noted interval (weekly) for safety purposes.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

In this study, disease is to be assessed using both RECIST 1.1 and the Modified RECIST for Pleural Tumors. This means that pleural tumors must be assessed using BOTH methods. RECIST 1.1 criteria are outlined in Sections 10.1-10.2. In addition, modified RECIST measurements as determined by six pleural thickness measurements perpendicular to the chest wall are to be obtained and incorporated into determination of objective status as outlined in Section 10.5. *(55)*

10.1 Measurability of lesions

a. **Measurable disease**

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to <1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.
2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.
3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective status at each disease evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).
2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.
4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.
6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.
7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Modified RECIST

Modified RECIST for Pleural Tumors: Response is to be assessed both via RECIST and modified RECIST for pleural tumors. *(54)*

For RECIST 1.1, the definitions outlined in Section 10.1 must be followed. The longest diameter of the pleural lesion, as defined in Section 10.1.a.1, must be recorded in the target lesion section of the RECIST and Modified RECIST Baseline Tumor Assessment Form (Form #35990) and the Follow Up Tumor Assessment Form-RECIST and Modified RECIST (Form #23757). If a longest diameter that fulfills the criteria outlined in Section 10.1.a.1 cannot be obtained, then it should be recorded in the non-target lesion section of the respective forms.

In addition, for modified RECIST, measurements based on the sum of 6 CT cuts in the pleura perpendicular to the chest wall are to be obtained via the description below and applied (along with unidimensional measurements from other non-pleural lesions) to

standard RECIST criteria (sum of 6 = one univariate diameter). The six pleural thickness measurements are to be documented on the RECIST and Modified RECIST Baseline Tumor Assessment Form (Form #35990) and the Follow Up Tumor Assessment Form-RECIST and Modified RECIST (Form #23757).

Tumor thickness perpendicular to the chest wall or mediastinum should be measured in two positions at three separate levels on transverse cuts of the CT scan. The sum of the six measurements defines a pleural unidimensional measure. Transverse cuts at least 1 cm apart and related to anatomical landmarks in the thorax should be chosen to allow for reproducible assessment at later time points. If measurable tumor is present, transverse cuts in the upper thorax, above the level of the division of the main bronchi are preferred. At reassessment, pleural thickness should be measured at the same position at the same level and by the same observer. This is not necessarily the greatest tumor thickness at that level. Nodal, subcutaneous and other measurable lesions should be measured unidimensionally as per the RECIST criteria. Unidimensional measurements are added to obtain the total tumor measurement.

10.6 Progression-free survival

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined in above), or death due to any cause. Patients last known to be alive and progression free are censored at date of last contact.

10.7 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Phase I Run-In

This study will initially be open in limited institutions, with an expected accrual of 10-20 patients in the Phase I portion of the trial. The Phase II portion of the trial will be initiated Groupwide. Based on data from M.D. Anderson in similar patient populations the estimated accrual rate is 4 patients/month.

11.2 Phase I Details

Phase I Study: Section 7.4 provides the details of the study design for the Phase I portion of the study. The Phase I study will be a limited dose-de-escalation study with two possible doses of cediranib:

Dose levels	0	-1
Cediranib (mg/daily)	30	20

The primary objective of this study is to determine the maximum tolerated dose (MTD) of cediranib used in combination with cisplatin and pemetrexed (CP) in chemonaive patients with malignant pleural mesothelioma (MPM). The regimen will be considered safe and the MTD determined if the dose-limiting toxicity rate of cediranib + CP is ≤ 33%.

11.3 Phase II Trial

Phase II Study: The primary objective of the Phase II portion of this study is to evaluate the efficacy of cediranib in combination with cisplatin and pemetrexed in comparison with cisplatin, pemetrexed and placebo in chemonaive patients with malignant pleural mesothelioma (MPM). Based on a previous study it is assumed that the regimen would not be promising if the true median PFS were ≤ 6 months, but would be of considerable interest if the true median PFS were ≥ 10 months (corresponding to a 1.66 hazard ratio). *(2)* Ninety-six patients will be accrued over an estimated 24 months. With an additional 9 months of follow-up, this design has 83% power to detect 66% improvement in median PFS at the 0.1 level.

11.4 Analysis plan for Phase II study

Primary analyses will be performed on an intent-to-treat basis. A stratified log-rank test at the 0.1 level will be used to test the primary hypothesis.

Once 50% of the expected events in the control arm have occurred (21 events at ~ 18 months after study opens), an interim analysis of the primary endpoint will be performed with the intent of testing the alternative hypothesis (e.g. terminate early if a 1.66 hazard ratio is deemed to be highly unlikely [$p<0.005$]).

Secondary analyses include the comparison of overall survival, response, and toxicity between study arms. A stratified log-rank test will be used to compare overall survival; a stratified chi-square test will be used to compare response and toxicity between the two arms. This design has 73% power to detect a 66% improvement in median survival time from 12 to 20 months using a 0.10 level test.

Additionally, this design has 83% power to detect > 20% difference in toxicity rates assuming an unacceptable toxicity rate > 33%, for any given toxicity (also using a 1-sided 0.1 level test). Within each arm, any toxicity occurring with at least a 5% probability is likely to be seen at least once (91% chance).

Forty-eight patients/arm will be sufficient to estimate the 6-month overall survival probability and individual toxicity proportions to within at least 14% (95% confidence interval).

Assuming 80% of participants will have measurable disease (as defined by RECIST), approximately 38 patients/arm will be evaluable for response. Seventy-six patients with measurable disease has 81% power to detect at least a 27% increase in response rates with cediranib using a 1-sided 0.10 level test. Thirty-eight patients/arm will be sufficient to estimate the response rate (confirmed and unconfirmed complete and partial responses) to within at least 16% (95% confidence interval). The disease control rate (confirmed and unconfirmed complete and partial responses and stable disease) will also be assessed.

In addition, an exploratory analysis of response and progression-free survival using definitions per modified RECIST criteria for pleural tumors will be performed.

11.5 Sample Size and Power Justification for Primary Endpoint

Assuming sufficient tissue for pathology review is received from 90 patients, this would be sufficient to estimate the rate of agreement between the local pathologist and the central pathology reviewer to within at least 11% (95% confidence interval).

Correlative studies will assess potential relationships between potential biomarkers (yet to be defined) involving angiogenesis, cediranib, pemetrexed and cisplatin and clinical and toxicity outcomes, utilizing available tumor tissue and plasma specimens. Due to the limited sample size in a Phase II setting, correlative studies will be considered exploratory in nature and will be used to formulate hypotheses that can be tested using correlative data in larger patient cohorts.

11.6 Analysis of Primary Endpoint

The Phase I portion of the trial will employ careful adverse event monitoring as previously established for regimens where there are limited or no pre-existing data for the specific combination under study, but where combination data for the targeted agent plus other chemotherapy regimens suggest that full doses of the study combination can be safely administered. Adverse event monitoring will performed by the Study Coordinator, Study Statistician and the Disease Committee Chair and include weekly toxicity reports and bi-weekly conference calls. A temporary closure will occur prior to opening this study for the Phase II portion in order to assess dose and to evaluate the safety profile more fully prior to implementation of the Phase II trial.

11.7 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the randomized Phase II portion of the study. The Committee consists of four members from outside of the Southwest Oncology Group, 3 Southwest Oncology Group members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the Southwest Oncology Group Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

Central pathology review will be performed on this study. The purpose of this review is to confirm diagnosis.

All patients are required to submit tissue for the purpose of this review. Instructions for tissue submission are located in Section 15.2a.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than ten working days prior to planned start of treatment). **NOTE: No open label OR blinded starter supplies will be available for this study.** Initial patient-specific clinical supplies of cediranib (Phase I) or cediranib/placebo (Phase II) will be shipped from the Pharmaceutical Management Branch (PMB) to the registering investigator at the time of patient registration and should arrive within 7 to 10 days (see Section 3.1d).

13.2 OPEN Registration Requirements

The individual registering the patient must have completed the **S0905** Registration Worksheet (Form #44837). The completed form must be referred to during the registration but should not be submitted as part of the patient data.

OPEN will also ask additional questions that are not present on the **S0905** Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.3 Registration procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed from the CTSU members' web site OPEN tab, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.
- To perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

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

d. Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.4 Exceptions

Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Worksheet) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see **Section 14.3a** for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission

a. SWOG institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data includes the SWOG patient number, study ID and patient initials.

14.4 Data Submission Procedures

a. WITHIN 7 DAYS AFTER REGISTRATION:

Submit the following:

S0905 Prestudy Form (Form #39381)

RECIST 1.1 and Modified RECIST Baseline Tumor Assessment Form (Form #35990)

S0905 Baseline Abnormalities Form (Form #41007)

Radiology reports from all scans used to assess disease and document eligibility*

Pathology report*

*NOTE: These must be faxed (**see Section 14.3b**)

b. WITHIN 14 DAYS AFTER REGISTRATION:

Submit the following:

Tissue for pathology review (see Section 15.2a)

c. IF PATIENT CONSENTS, SUBMIT SPECIMENS FOR RESEARCH:

Submit the following:

Serum, plasma and buffy coat – samples may be batched (see Section 15.3a.1)

Whole blood – submit within 30 days after beginning treatment (see Section 15.3a.2)

Paraffin-embedded tissue - submit within 30 days after beginning treatment (see Section 15.3a.3)

d. PHASE I PORTION ONLY: AFTER EVERY WEEK DURING CYCLE 1:

Submit the web-based **S0905** Phase I Dose-Limiting Toxicity Rapid Reporting Form (Form #31896), which can be found on the CRA workbench (see **Section 14.3**). For further details regarding the rapid reporting system, see Section 15.1.

e. AFTER EVERY CYCLE ON TREATMENT:

Submit the following:

S0905 Treatment Form (Form #39146)

S0905 Adverse Event Form (Form #19062)

Patients on the Phase I portion will begin submitting the **S0905** Adverse Event Form (Form #19062) after Cycle 2 then after every cycle thereafter. Adverse events for Cycle 1 must be reported weekly using the **S0905** Phase I Dose-Limiting Toxicity Rapid Reporting Form (Form #31896).

f. AFTER EVERY DISEASE ASSESSMENT (see Section 9.0):

Submit the following:

Follow Up Tumor Assessment Form - RECIST 1.1 and Modified RECIST (Form #23757)

Radiology reports from all scans used to assess disease

g. ONCE OFF TREATMENT SUBMIT EVERY 6 MONTHS FOR THE FIRST 2 YEARS, THEN AT THE END OF YEAR 3:

Submit the following:

Lung Carcinoma Follow Up Form (Form #32426).

Follow Up Tumor Assessment Form - RECIST 1.1 and Modified RECIST (Form #23757) until progression of disease

Radiology reports from all scans used to assess disease

h. WITHIN 14 DAYS AFTER PROGRESSION/RELAPSE:

Submit the following:

Lung Carcinoma First Site(s) of Progression or Relapse Form (Form #9469)

Follow-Up Tumor Assessment Form - RECIST 1.1 and Modified RECIST (Form #23757) documenting date, site and method used to determine relapse.

If the patient is off protocol treatment, submit the Lung Carcinoma Follow Up Form (Form #32426) with notice of first relapse or progression section completed.

i. WITHIN 14 DAYS AFTER DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice (Form #52393)

S0905 Treatment Form (Form #39146)

S0905 Adverse Event Form (Form #19062)

S0905 Phase I Dose-Limiting Toxicity Rapid Reporting Form (Form #31896) – if patient is on the Phase I portion and did not begin Cycle 2 of treatment

j. WITHIN 4 WEEKS AFTER KNOWLEDGE OF DEATH:

Submit the following:

Notice of Death (Form #49467)

Off Treatment Notice (Form #52393) – if patient is still on treatment

Lung Carcinoma Follow Up Form (Form #32426) – if patient is already off treatment

15.0 SPECIAL INSTRUCTIONS

15.1 Rapid Reporting

RAPID REPORTING OF TREATMENT-RELATED DOSE-LIMITING TOXICITIES FOR PHASE I PORTION OF TRIAL

Participation in the Phase I portion of the trial requires weekly reporting of dose-limiting toxicities on patients who have initiated treatment. **These toxicities must be reported using the web-based S0905 Phase I Dose-Limiting Toxicity Rapid Reporting Form (Form #31896), which can be found on the CRA workbench (see *Section 14.3*).**

Institutional participation in the Phase I portion of the trial requires the identification of a contact CRA and back-up CRA. **Prior to registration of the first patient, each institution must provide the contact and back-up CRA names, e-mail addresses, and phone numbers to the SWOG Data Operations Center.** Institutions will be responsible for keeping this information up-to-date and must notify the study Data Coordinator (Brian Zeller, brianz@crab.org, 206/652-2267) of any changes.

The contact CRA and back-up CRA will receive weekly e-mails including a list of the dose-limiting toxicity forms that are overdue, currently due, or due in the next week. These e-mails will include a reply-to address and phone number to contact the Data Operations Center when questions arise.

Upon activation of the Phase I portion of the study, participating institutions will receive an e-mail with information on current dose level, as well as specifications for e-mail and conference call communication among investigators participating in the Phase I portion.

15.2 Specimens for Pathology Review

Specimens for pathology review specimens for pathology review (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (Required):

a. Specimens must be collected for central pathology review (see Section 12.0) at the following times and submitted (see Sections 9.1-9.2):

   1. Submit 1-2 stained slides containing tumor tissue from surgery or biopsy, or malignant pleural mesothelioma tissue cells from a pleural effusion (a cell button in paraffin) within 14 days after registration. With additional patient consent, cell buttons submitted for pathology review may be banked for future use.

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp), or via the link on the **S0905** protocol abstract page on the SWOG website (www.swog.org).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

15.3 Specimens for Correlative Studies and Banking

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201)(Optional):

a. With patient's consent, specimens must be collected at the following times and submitted (see Sections 9.1-9.2):

1. Instructions for serum, plasma and buffy coat:

Collect blood at the following time points:

- Prior to initiating treatment on Day 1 and, if possible, 8 hours after first dosing
- Days 8 and/or 15
- Day 22 (Cycle 2, Day 1), then every 21 days up to and including Cycle 6, Day 1
- Cycle 7, Day 1, and then every 6 weeks while on maintenance cediranib/placebo
- When the patient is removed from protocol treatment

Serum collection

- Collect 7.5 mL of blood in a S-Monovette
- After allowing 30 minutes for blood coagulation (no longer than 60 minutes), the sample is centrifuged at 3000 G for 15 minutes.
- Serum is pipetted in 1mL aliquots into three white labeled Nalgene cryovials.
- Clearly label tubes as "serum".
- **Note**: Sample must be processed within 2 hours of collection. Hemolyzed, lipemic, or icteric specimens may cause erroneous results.

Plasma and buffy coat collection

- Collect two (2) x 5 mL of blood into two (2) K2-EDTA DB Vacutainer collection tubes pre-cooled in an ice bath.
- Gently invert five to six times to ensure adequate mixing and prevent coagulation.
- Cool the tubes immediately in an ice bath.
- Centrifuge at 800 G for 10 minutes within 30 minutes of collection.
- Plasma is pipetted in 1 mL aliquots into four (4) red labeled Nalgene cryovials.
- Buffy coat cells should be removed separately from the plasma and placed in a labeled cryo tube.
- Clearly label tubes as "buffy coat" or "plasma".

Storage and Shipment

Samples must be stored as soon as possible at -70°C until shipment. Specimens may be batched. They must be shipped frozen on dry ice by overnight carrier. Follow the general submission instructions located in Section 15.3b below.

2. Instructions for whole blood:

Collect blood at the following time point:

Prior to initiating treatment on Day 1

Collection

- Collect blood in 9 or 10 mL polypropylene tubes containing the anticoagulant EDTA
- SARSTEDT Monovette® EDTA KE (9 mL), Part # 02.1333.001

Or

- Becton-Dickinson Vacutainer™ K2E (10 mL), Part # 367525

or

- Greiner Bio-One Vacuette® K3E EDTA K3 (9 mL), Part 455036

- Blood tubes must be gently inverted several times after collection to ensure thorough mixing of EDTA with the sample to prevent clotting.
- **Glass tubes MUST NOT be used** as they may break transport and freeze-thaw cycles.
- **Heparin MUST NOT be used as an** anticoagulant as it may interfere with downstream genotyping methodology.

Storage and Shipment

Samples must be refrigerated or frozen as soon as possible until shipment. See the chart below for options regarding storage and shipping. Also follow the general submission instructions located in Section 15.3b below.

Option	Storage Temperature at Treatment Site	Maximum Duration of Storage at Treatment Site	Transport Temperature	Delivery Time
1	+ 4°C (fridge)	24 hours	0 - 4°C (ice blocks)	24 hours
2	+ 4°C (fridge)	24 hours	Less than -20°C (dry ice)	24-72 hours
3	-20°C (freezer) or -70°C	Up to 1 month	Less than -20°C (dry ice)	24-72 hours

- If blood samples are to be frozen for storage at -20°C or less, **non-frost free freezers** must be used to prevent repeated freeze-thaw of blood which may reduce yield and quality of the DNA obtained.
- **Samples must not be thawed and then re-frozen at any point.**

3. Instructions for paraffin embedded tissue:

   Submit 1-2 paraffin-embedded tissue blocks containing formalin-fixed tumor from time of diagnosis (or subsequent, but prior to therapy). Paraffin blocks may be processed according to standard institutional protocols. If a tissue block is unavailable or unable to be sent, 10-15 unstained slides or malignant pleural mesothelioma cells from a pleural effusion (a cell button in paraffin) are acceptable as an alternate.

   Archival paraffin blocks/slides should be sent at **ambient temperature** following the general specimen submission instructions located in Section 15.3b, within 30 days after beginning treatment.

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp), or via the link on the **S0905** protocol abstract page on the SWOG website (www.swog.org).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent (hereinafter referred to as "Agent"), cediranib/placebo, used in this protocol is provided to the NCI under a Clinical Trials Agreement (CTA) between AstraZeneca (hereinafter referred to as "Collaborator") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent in this study:

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

2. For a clinical protocol where there is an investigational Agent used in combination with another investigational Agent, each the subject of different CTAs or CRADAs, 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 must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which 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 to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

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

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

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

5. Any data provided to the Collaborator for Phase III 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 for immediate delivery to the Collaborator for advisory review and comment prior to submission for publication. Collaborator 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 the Collaborator's intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to the Collaborator 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 presentation must also be forwarded to CTEP prior to release.

Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX: 301/402-1584
E-mail: anshers@mail.nih.gov

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

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 18.1 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov. An AdEERS report must be submitted to the SWOG Operations Office by one of the following methods:

Electronically submit the report via the AdEERS Web-based application located at http://ctep.cancer.gov, or

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

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via AdEERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, a 24-hour notification phoned in, must be entered electronically into AdEERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1 or 16.2, as applicable.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 16.1 for the Phase I portion and Table 16.2 for the Phase II portion. The investigational agent used in this study is cediranib/placebo. If there is any question about the reportability of an adverse event or if on-line AdEERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:

Phase I Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of an Investigational Agent (cediranib/placebo) in this study (Phase I portion).

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

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND or non-CTEP IND require reporting as follows:**

AdEERS 24-hour notification (**via AdEERS for CTEP IND agents**; via email to [Group] AE Coordinator for agents in non-CTEP IND studies) followed by complete report within 5 calendar days for:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

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

Please see exceptions below under section entitled "Additional Instructions or Exceptions."

March 2005

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

Table 16.2:

Phase II and III Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of an Investigational Agent (cediranib/placebo) in this Study (Phase II portion).

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

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND or Non-CTEP IND require reporting as follows:**
AdEERS 24-hour notification (**via AdEERS for CTEP IND agents; via email to *adr@swog.org* for agents in non-CTEP IND studies**) followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

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

Please see exceptions in f. below, "Additional Instructions or Exceptions."

March 2005

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

Expedited AE reporting timelines defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within <u>24 hours</u> of learning of the event followed by a complete AdEERS report within <u>5 calendar days</u> of the initial 24-hour report.
- "10 calendar days" - A complete AdEERS report on the AE must be submitted within <u>10 calendar days</u> of the investigator learning of the event.

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

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

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

f. Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase II and III Trials Utilizing an Agent under a CTEP-IND:

1) Group-specific instructions.

Submission of the on-line AdEERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent by fax to 210-614-0006. Note, however, that any documents checked in the Additional Information section of the AdEERS report must be submitted to CTEP per the instructions on that AdEERS web page.

2) For this study, the adverse events listed below do **not** require expedited reporting via AdEERS:
- Grade 4 myelosuppression

g. Reporting secondary AML/ALL/MDS

1. All cases of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported in AdEERS.

i. In protocols using CTCAE Version 4.0 for SAE reporting, three options are available to describe treatment-related events:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome. NOTE: The only grading option for "Myelodysplastic syndrome" is Grade 4, life-threatening. If reporting MDS that is other than Grade 4, use “Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, (specify,__)” and insert MDS as the specify term.
- Treatment related secondary malignancy

ii. In protocols using CTCAE Version 3.0 for SAE reporting, the event(s) can be reported as “Secondary malignancy-Other (specify, ___)”. Report MDS as “Myelodysplasia,” in the BLOOD/BONE MARROW category.

iii. Secondary malignancies <u>other than</u> AML/ALL/MDS that are related to protocol treatment must also be reported in AdEERS.

iv. Non-treatment related cases of AML/ALL/MDS must be reported as follows:

In protocols using CTCAE Version 4.0 for SAE reporting, report as "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify"

In protocols using CTCAE Version 3.0 for SAE reporting, report MDS as "Myelodysplasia" and Leukemias as "Blood/Bone Marrow - Other (Specify, __)"

For more information see:
http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers

2. The following supporting documentation must also be submitted within 30 days:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

Submit the Report and documentation to:

Investigational Drug Branch **and** by electronically submitting the report via the AdEERS web-based application located at http://ctep.cancer.gov, or in the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.	SWOG ATTN: SAE Program 4201 Medical Drive, Suite 250 San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.0.

All serious adverse events must also be reported to the local Institutional Review Board (IRB). Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- Concurrent administration: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- Sequential administration: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: Grade the event using the NCI CTCAE version specified.

Step 3: Determine whether the adverse event is related to the protocol therapy (investigational or commercial). Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: Review Tables 16.1 and 16.2 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.

Step 6: Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to the instructions in Table 16.1 (Phase I) or Table 16.2 (Phase II).

18.2 Appendix Deleted 11/29/10

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18.3 Intake Calendar

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #_____**

Institution/Affiliate _____ Physician _____

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature:_____

18.4 Medications that may cause QTc prolongation

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

Compound	Compound Half Life	QTc Prolongation Association/ Concurrent Administration	Possible Washout Period - Hours	Possible Washout Period - Days
Alfuzocin	~10 hours	Some/Use Discretion		7
Amantadine	17 +/- 4 hours (10-25)	Some/Use Discretion		4
Amiodarone ** (cordarone)	**58 days (15-142) 36 days (active metabolite)**	**Strong/Prohibited**		**14**
Amitriptyline*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Amoxapine	~ 8 hours	Weak/At usual doses	40 hours	2 days
Ampicillin	1 to 1.5 hours	Weak/At usual doses		
Arsenic trioxide	**Not characterized; may be weeks**	**Strong/Prohibited**		
Azithromycin	40 hours	Some/Use Discretion		
Bepridil	**42 hr (26-64)**	**Strong/Prohibited**		**10**
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $T_{1/2}$=7-10 hour)	Some/Use Discretion	48	
Chloroquine	**1. 6 to 60 days; mean 20 days**	**Strong/Prohibited**		
Chlorpromazine	**2. 30 +/- 7 hours**	**Strong/Prohibited**		**7**
Ciprofloxacin	3.5 to 4.5 hours	Weak/At usual doses		
Cisapride	**6 – 12 hour, up to 20 hour**	**Strong/Prohibited**	**60**	
Citalopram		Weak/At usual doses		
Clarithromycin	Non linear PK3-4 hr (250mg Q12) **5-7 hr (500mg Q12)**	**Strong/Prohibited**	**36**	**3**
Clomipramine	~ 21 hours	Weak/At usual doses		
Clozapine	12 hours at steady state	Some/Use Discretion		
Desipramine*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Disopyramide	**6.7 hr (4-10)**	**Strong/Prohibited**	**36**	
Dofetilide	**10 hr**	**Strong/Prohibited**	**48**	
Dolesetron	8.1 hr	Some/Use Discretion		

Domperidone	**7-8 hr**	**Strong/Prohibited**	**48**	
Doxepin*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Droperidol	**2.2 hours**	**Strong/Prohibited**	**10**	
Erythromycin	*** Each salt form has different Half life***	**Strong/Prohibited**		
Felbamate	20-23 hr	Some/Use Discretion		5
Flecainide	20 hr (12-27)	Some/Use Discretion		5
Fluconazole	~ 30 hours	Weak/At usual doses		
Foscarnet	87.5+/-41.8 hours *distribution and release from bone*	Some/Use Discretion		20
Fosphenytoin	12-29 hr	Some/Use Discretion		6
Galantamine		Weak/At usual doses		
Gatifloxacin	7-14 hr	Some/Use Discretion	48	
Gemifloxacin	7 hours	Some/Use Discretion	48	
Granisetron	3 to 4 hours	Some/Use Discretion		
Grepafloxacin	16 hr	Some/Use Discretion		3
Halofantrine	**6-10 days (variable among individual)**	**Strong/Prohibited**		**45**
Haloperidol	**18 +/-5 hr**	**Strong/Prohibited**		**5**
Ibutilide	**6 hours (2-12) * variable among subject***	**Strong/Prohibited**	**36**	**3**
Imipramine*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Indapamide	14 hours (biphasic elimination)	Some/Use Discretion		3
Isradipine	8 hours (multiple metabolites)	Some/Use Discretion	48	
Itraconazole	20 hours, increasing to 40 hours	Weak/At usual doses		
Ketoconazole	2 hours, increasing to 8 hours	Weak/At usual doses		
Levofloxacin	6-8 hours	Some/Use Discretion	48	
Levomethadyl	**Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM**	**3. Strong/Prohibited**	**4.**	**5. 20**
Lithium	24 hour (10-50)	Some/Use Discretion		7
Mefloquine	13 to 24 days	Weak/At usual doses		

Mesoridazine	**24-48 hours (animal study)**	**Strong/Prohibited**		**10**
Methadone	**15-30 hours**	**Strong/Prohibited**		**7**
Mexiletine	>10 hours	Weak/At usual doses		
Moexipril/HCTZ	2-9 hour (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	Some/Use Discretion	48	
Moxifloxacin	12 +/-1.3 hours	6. Some/Use Discretion	7. 72	8.
Naratriptan	6 hours		36	
Nicardipine	~ 2 hour post IV infusion	Some/Use Discretion	12	
Nortriptyline*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Octreotide	1.7 hours	Some/Use Discretion	12	
Ofloxacin	5 to 7.5 hours	Some/Use Discretion		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)	Some/Use Discretion		1 to 3
Paroxetine		Weak/At usual doses		
Pentamidine	**6.4+/-1.3 hours**	**Strong/Prohibited**	**36**	
Pimozide	**55 hours**	**Strong/Prohibited**		**10**
Procainamide	**3-4 hour for PA and NAPA (active metabolite)**	**Strong/Prohibited**	**24**	**3**
Protiptyline*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Quetiapine	6 hours	Some/Use Discretion	36	
Quinidine	**6-8 hours in adult; 3-4 hours in children**	**Strong/Prohibited**	**36**	
Quinine	4-5 hours	Weak/At usual doses		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T ½ =21-30 hours (extensive to poor metabolizer)	Some/Use Discretion		4
Roxithromycin		Some/Use Discretion		
Salmeterol	5.5 hours (only one datum)	Some/Use Discretion	36	
Sertraline	~ 26 hours	Weak/At usual doses		
Solifenacin	40 to 68 hours	Weak/At usual doses		
Sotalol	**12 hours**	**Strong/Prohibited**	**72**	

Sparfloxacin	**20 hours (16-30)**	**Strong/Prohibited**		**4**
Sumatriptan	2.5 hours		12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant	Some/Use Discretion		7
Tamoxifen	5-7 days (biphasic)	Some/Use Discretion		30
Telithromycin	2-3 hr	Some/Use Discretion	24	
Thioridazine	**20-40 hours (Phenothiazines)**	**Strong/Prohibited**		**7**
Tizanidine	2.5 hours	Some/Use Discretion	12	
Trimethoprim/sulfa	6 to 17 hours	Weak/At usual doses		
Trimipramine	~ 23 hours	Weak/At usual doses		
Vardenifil	4 to 5 hours	Some/Use Discretion		
Venlaflaxine	5 +/-2 hours for parent comp. 11+-2 hours for OVD (active metabolite)	Some/Use Discretion	60	
Voriconizole	6 hours; dose dependent	Some/Use Discretion		
Ziprasidone	7 hr	Some/Use Discretion	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	Weak/At usual doses	18	

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

**** Patients should discontinue amiodarone and switch to an anti-arrhythmic agent that does not interfere with the protocol. Prior to and after the 14 day washout period, baseline EKG's should be checked. If the QTc interval is normal, then proceed to enroll the patient onto the trial.**

References:

1. **Physician's Desk Reference 2002**
2. **Facts and Comparisons (update to June 2005)**
3. **The Pharmacological Basis of Therapeutics 9th Edition, 1996**
4. **ArizonaCERT Center for Education and Research on Therapeutics, http://torsades.org/medical-pros/drug-lists/drug-lists.htm**

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

18.5 New York Heart Association Class

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, & 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.

18.6 Emergency Unblinding Guidelines

a. **General Considerations**

The randomized regimen for this study includes a blinded drug, which is either cediranib or placebo. During the course of this study it may become necessary to identify (or unblind) a patient's treatment assignment. The circumstances that will warrant emergency unblinding and the procedure for emergency unblinding are described in this Appendix.

b. **Criteria for Emergency Unblinding**

In general, treatment assignments will not be emergency unblinded unless there is a compelling medical or ethical reason that the treatment should be identified. In most circumstances it will be appropriate to treat the patient or person who received blinded drug as though he or she received cediranib, irrespective of the drug actually received. Therefore, emergency unblinding should seldom be necessary.

The following events MAY require emergency unblinding of treatment assignments in this study:

1. A compelling medical need as determined by a physician, e.g., existence of a condition for which knowledge of the patient's treatment assignment is necessary for the selection of appropriate care.

2. Administration of blinded drug to a person other than the patient.

c. **Procedure for Emergency Unblinding**

Emergency unblinding of treatment assignments for patients on this study will be performed by the Washington Poison Center (WPC), upon approval from a designated physician (either one of the WPC's resource physicians or Dr. Anne Tsao). The procedure for emergency unblinding the treatment assignment for a patient on this study is as follows:

1. All requests for emergency unblinding must be made by the registering physician or his/her designee.

2. Call the WPC collect at 206/526-2121 from outside Washington State or toll free at 800/222-1222 from within Washington State. The WPC is accessible 24 hours per day, 365 days per year.

3. The person calling the WPC must be prepared to provide the following information:

Study number (**S0905**)

Southwest Oncology Group Patient Number (e.g., "999999")

Patient Initials

Name and telephone number of the caller

Reason emergency unblinding is thought to be required

4. The WPC will contact one of its resource physicians and provide the information received from the caller. If none of the WPC's resource physicians can be contacted, then the WPC will contact Dr. Anne Tsao. The contacted physician will evaluate the need for emergency unblinding and provide the WPC either approval to unblind or a recommendation for treatment, if any, while maintaining blinding. The WPC will then call the person who initiated the unblinding request and tell him/her either the treatment assignment or the resource physician's treatment recommendation.

5. If the WPC is unable to contact any of its resource physicians or Dr. Tsao within three hours after receiving the request for emergency unblinding, then the WPC will notify the person who initiated the unblinding request that treatment assignment will not be unblinded at that time and treatment of the patient or person who received blinded drug should proceed as if the blinded drug is cediranib. In such cases, the WPC will continue to attempt to contact the resource physicians, and when one of them is contacted, will proceed as in #4 above.

6. Any patient whose treatment assignment is emergency unblinded will receive no further blinded drug, but should continue all other protocol treatment if his/her medical condition permits.

7. Unblinding of treatment assignments for any reason must be documented on the Off Treatment Notice.

Questions regarding the unblinding may be directed to any of the following resource physicians:

Anne S. Tsao, M.D.
MD Anderson Cancer Center
1515 Holcombe Boulevard
Unit 432
Houston, Tx 77030
Phone: 713/792-6363
E-mail: astsao@mdanderson.org

Anne Schott, M.D.
Southwest Oncology Group
24 Frank Lloyd Wright Drive
P.O. Box 483
Ann Arbor, MI 48106
Phone: 734/998- 7172
E-mail: aschott@umich.edu

Washington Poison Center
Phone: 206/526-2121

18.7 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

CYP2D6	
SUBSTRATES	
Amitriptyline (hydroxylation) Amphetamine Betaxolol Bisoprolol Brofaromine Buturolol Bupropion Captopril Carvedilol Cevimeline Chlorpheniramine Chlorpromazine Cinnarizine Clomipramine (hydroxylation) Clozapine (minor pathway) Codeine (hydroxylation, o-demelhylation) Cyclobenzaprine (hydroxylation) Cyclophosphamide Debrisoquin Delavirdine Desipramine Dexfenfluramine Dextromethorphan (o-demethylation) Dihydrocodeine Diphenhydramine Dolasetron Donepezil Doxepin Encainide Fenlluramine Flecainide Fluosetine (minor pathway) Fluphenazine Haiofantrine Haioperidol (minor pathway) Hydrocodone Hydrocortisone Hydroxyamphetamine lmipramine (hydroxylation) Labetalol Loratadine Maprotiline m-Chlorophenylpiperazine (m-CPP) Meperidine Methadone	Methamphetamine Metoclopramide Metoprolol Mexitetine Mianserin Mirtazapine (hydroxylation) Molindone Morphine Nortriptyline (hydroxylation) Olanzapine (minor, hydroxymethylation) Ondansetron Orphenadrine Oxycodone Papaverine Paroxetine (minor pathway) Penbutolol Pentazocine Perhexiline Perphenazine Phenformin Pindolol Promethazine Propafenone Propranolol Quetiapine Remoxipride Risperidone Ritonavir (minor) Ropivacaine Selegiline Sertindole Sertratine (minor pathway) Sparteine Tamoxifen Thioridazine Tiagabine Timolol Tolterodine Tramadol Trazodone Trimipramine Tropisetron Venlafaxine (o-desmethylation) Yohimbine

INHIBITORS	
Amiodarone	Methadone
Celecoxib	Mibefradil
Chloroquine	Moclobemide
Chlorpromazine	Nortluoxeline
Cimelidine	Paroxetine
Citalopram	Perphenazine
Clomipramine	Propafenone
Codeine	Quinacrine
Deiavirdine	Quinidine
Desipramine	Ranitidine
Dextropropoxyphene	Risperidone (weak)
Diitiazem	Ritonavir
Doxorubicin	Sertindole
Entacapone (high dose)	Sertraline (weak)
Fluoxetine	Thioridazine
Fluphenazine	Vaiprolc acid
Fluvoxamine	Venlafaxine (weak)
Haloperidol	Vinblastine
Labetalol	Vincristine
Lobeline	Vinorelbine
Lomustine	Yohimbine

CYP3A3/4	
Substrates	
Acetaminophen	Chlorpromazine
Aifentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citałopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clonazepam
Androsterone	Clozapine
Antipyrine	Cocaine
Astemizole	Codeine (demethylation)
Atorvastatin	Cortisol
Benzphetamine	Cortisone
Bepridil	Cyclobenzaprine (demethylation)
Bexarotene	Cyclophosphamide
Bromazepam	Cyclosporine
Bromocriptine	Dapsone
Budesonide	Dehydroepiandrostendione
Bupropion (minor)	Delavirdine
Buspirone	Desmethyldiazepam
Busutfan	Dexamethasone
Caffeine	Dextromethorphan (minor, N-demethylation)
Cannabinoids	Diazepam (minor; hydroxylation, N-demethylation)
Carbamazepine	
Cevimeline	
Cerivastatin	
Digitoxin	Nefazodone
Diltiazem	Nelfinavir
Disopyramide	Nevirapine
Docetaxel	Nicardipine
Dolasetron	Nifedipine
Donepezil	Niludipine

Doxorubicin Doxycycline Dronabinol Enalapril Erylhromycin Estradiol Ethinyl estradiol Ethosuximide Etoposide Exemestene Dofetilide (minor) Felodipine Fentanyl Fexotenadine Finaxteride Fluoxetine	Nimodipine Nisoldipine Nitrendipine Omeprazole (sulfonation) Ondansetron Oral contraceptives Orphenadrine Paclitaxel Pantoprazole Pimozide Pioglitazone Pravastatin Prednisone Progesterone Proguanil Propafenone
FLUTAMIDE	
Substrates	
Glyburide Granisetron Halofantrine Hydrocortixone Hydroxyarginine Ifosfamide Imipramine Indinavir Isradipine Itraconazole Ketoconazole Lansoprazole (minor) Letrozole Levobupivicaine Lidocaine Loratadine Losartan Lovastatin Methadone Mibefradil Miconazole Midazolam Mifepristone Mirtazapine (N-demethylation) Montelukast Navelbine Toremifene Trazodone Tretinoin Triazolam Troglitazone Troleandomycin Venlafaxine (N-demethylation) Verapamil Vinblastine	Quercetin Quetiapine *Quinidine* Quinine Repaglinide Retinoic acid Rifampin Risperidone Ritonavir Salmeterol Saquinavir Sertindole Sertraline Sibutramine Sildenafil citrate Simvastatin Sirolimus Sufentanil Tacrolimus Tamoxifen Temazepam Teniposide Terfenadine Testosterone Tetrahydrocannabinol Theophylline Tiagabine Tolterodine Vincristine Warfarin (R-warfarin) Yohimbine Zaleplon (minor pathway) Zatoestron Zileuton Ziprasidone Zolpidem Zonisamide

INDUCERS	
Carbamazepine Dexamethasone Ethosuximide Glucocorticoids Griseofulvin Nafcillin Nelfinavir Nevirapine Oxcarbazepine Phenobarbital Phenylbutazone	Phenytoin Primidone Progesterone Rifabutin Rifampin Rofecoxib (mild) St John's wort Sulfadimidine Sulfinpyrazone Troglitazone
INHIBITORS	
Amiodarone Anastrozole Azithromycin Cannabinoids Cimetidine Clarithromycin Clotrimazole Cyclosporine Danazol Delavirdine Dexamethasone Diethyldithiocarbamate Diltiazem Dirithromycin Disulfiram Entacapone (high dose) Erythromycin Ethinyl estradiol Fluconazole (weak) Fluoxetine Fluvoxamine Gestodene Grapefruit juice Indinavir Isoniazid Itraconazole	Ketoconazole Metronidazole Mibefradil Miconazole (moderate) Nefazodone Nelfinavir Nevirapine Norfloxacin Norfluoxetine Omeprazole (weak) Oxiconazole Paroxetine (weak) Propoxyphene Quinidine Quinine Quinupristin and dalfopristin Ranitidine Ritonavir Saquinavir Sertindole Sertraline Troglitazone Troleandomycin Valproic acid (weak) Verapamil Zafirlukast Zileuton

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371