Clinical Center # 11-C-0200
CTEP # 8875

A Phase II Trial in Which Patients With Metastatic Alveolar Soft Part Sarcoma Are Randomized to Either Sunitinib or Cediranib Monotherapy, With Cross-Over at Disease Progression

Abbreviated Title: Ph II Cediranib Sunitinib in ASPS

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NCI-Supplied Agents:	Cediranib (NSC 732208) Sunitinib malate (NSC 736511)
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PRÉCIS

Background:

- Alveolar soft part sarcoma (ASPS) is a rare, highly vascular tumor accounting for less than 1% of soft tissue sarcomas. There is no effective systemic treatment for patients with metastatic ASPS. Little is known with regards to relevant molecular markers as potential therapeutic targets.
- Cediranib (AZD2171) and sunitinib (SU011248), oral small molecule inhibitors of VEGF receptor tyrosine kinases, are showing preliminary evidence of activity in patients with ASPS.

Objectives:

- Part I: Determine the objective response rate (ORR) of single-agent cediranib and single-agent sunitinib malate in patients with advanced ASPS.
- Part II: Determine the ORR of cediranib in patients who progress on the sunitinib arm, and determine the ORR of sunitinib in patients who progress on the cediranib arm.
- Determine the progression-free survival (PFS) at 24 weeks for single-agent cediranib and single-agent sunitinib malate in patients with advanced ASPS.
- Perform pharmacokinetic analysis for cediranib.

Eligibility:

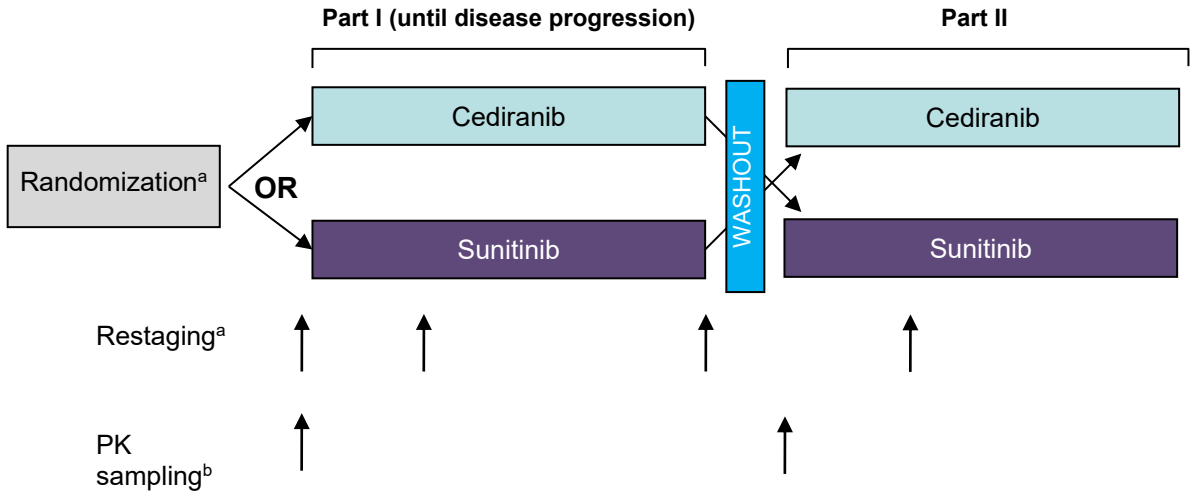
> ***Status Update: Patients enrolled after Amendment G (version dated 08/16/2013), will be evaluated and compared to the first 13 patients by the study statistician and the Principal Investigator. Patients with newly diagnosed ASPS with clinical evidence of disease progression will also be assessed separately.***

- Patients aged ≥ 16 years with histologically or cytologically confirmed metastatic ASPS.
- Patients must show evidence of objective disease progression per RECIST 1 on scans within the 6 month period immediately preceding enrollment. Both scans used to determine disease progression should have been obtained within this 6-month period.
- Patients with newly diagnosed, unresectable, measurable, metastatic ASPS who show clinical evidence of disease progression will be eligible.
- Patients must not have received treatment with any VEGF receptor tyrosine kinase inhibitor (e.g., cediranib, sunitinib, pazopanib, sorafenib); however, prior treatment with bevacizumab is allowed.

Design:

- Two sets of patients will be enrolled and assessed in separate cohorts: a) patients with non-newly diagnosed ASPS and b) patients with newly diagnosed ASPS.
- Part I: Patients will be randomized to receive cediranib (30 mg) or sunitinib malate (37.5 mg) orally, once a day in 28-day cycles. *As of Amendment Y (dated May 6, 2019), we have closed the cediranib arm of the newly diagnosed ASPS cohort due to inadequate activity per the statistical plan in Section 13; all newly diagnosed ASPS patients will be assigned to the sunitinib malate treatment arm.*
- Part II: At the time of disease progression, patients will cross over to the other treatment arm after a 2-week wash-out period. *As of Amendment Y (dated May 6, 2019), patients in the newly diagnosed ASPS cohort are not eligible to cross over to the cediranib treatment arm, which was closed due to inadequate activity.*
- Appropriate anatomic imaging studies will be performed at baseline and every 2 cycles for restaging.
- The study will be conducted using an optimal two-stage design to rule out an unacceptably low 15% clinical response rate (PR+CR) in favor of a modestly high response rate of 40%. The study will initially enroll 10 evaluable patients in each arm. If 0 or 1 of the 10 patients has a clinical response, then no further patients will be accrued. If 2 or more the first 10 patients have a response, then accrual continues to a total of 22 patients in each arm.

SCHEMA



Part I: Patients will be randomized to receive cediranib (30 mg) or sunitinib malate (37.5 mg) orally, once a day, in 28-day cycles. Part I is a two-stage design in which 10 patients are initially enrolled in each arm. If 0 or 1 of the 10 patients has a clinical response, then no further patients will be accrued. That treatment arm will be closed to the accrual of new patients and the crossover of patients who progressed on the other agent. If 2 or more the first 10 patients have a response, then accrual would continue until a total of 22 patients have enrolled in that arm.

Part II: At the time of disease progression (documented by RECIST 1), patients will cross over to the other treatment arm after a 2-week wash-out period (unless the other arm has been closed due to inadequate activity or unacceptable toxicity).

[a] Objective disease progression per RECIST 1 must be documented on scans within the 6 month period immediately preceding enrollment. Both scans used to determine disease progression should have been obtained within this 6-month period. Appropriate anatomic imaging studies will be performed at baseline (within 28 days prior to enrollment) and every 2 cycles on study for restaging.

[b] Blood samples for PK analyses will be collected in 4 cc EDTA (purple top) tubes pre-dose, and at the following time points prior to drug administration on that day: cycle 1 day 15, C2D1, C3D1, and C4D1. PK analysis will be performed only on samples from patients on cediranib (both as upfront therapy and following cross-over). No PK sampling and analysis will be done for patients receiving sunitinib.

As of Amendment Y (dated May 6, 2019), we have closed the cediranib arm of the newly diagnosed ASPS cohort due to inadequate activity per the statistical plan in Section 13. All newly diagnosed ASPS patients will be assigned to the sunitinib malate treatment arm; they will not cross over to the cediranib treatment arm, which was closed due to inadequate activity.

TABLE OF CONTENTS

1 STUDY OBJECTIVES

1.1 Primary Objectives

- Part I: Determine the objective response rate (ORR) of single agent cediranib and single-agent sunitinib malate in patients with advanced ASPS.
- Part II: Determine the ORR of cediranib in patients who progress on the sunitinib arm, and determine the ORR of sunitinib in patients who progress on the cediranib arm.

1.2 Secondary Objectives

- Determine the progression-free survival (PFS) at 24 weeks for single-agent cediranib and single-agent sunitinib malate in patients with advanced ASPS.
- Evaluate gene expression in tumor biopsies obtained at baseline and after treatment (at the Clinical Center, NCI only). *With Amendment H (version dated 11/20/2013), biopsies will no longer be performed as part of this study.*
- Perform pharmacokinetic analysis for cediranib.

2 BACKGROUND AND RATIONALE

2.1 Alveolar Soft Part Sarcoma (ASPS)

Alveolar soft part sarcoma (ASPS) is a rare tumor accounting for less than 1% of soft tissue sarcomas. The total number of new soft tissue sarcoma cases in the United States in 2010 is estimated to be 10,520 (American Cancer Society, 2010), which predicts approximately 100 new cases of ASPS in the United States annually. The rarity of this disease is exemplified by the number of cases of ASPS seen at major centers (Daigeler *et al*., 2008; Lieberman *et al*., 1989), such as 74 cases at MD Anderson from 1959 to 1998 (Portera *et al*., 2001) and 57 cases from a Japanese registry of 27 centers over a period of 25 years (Ogose *et al*., 2003).

ASPS occurs most frequently in patients between 15 and 35 years of age and is more prevalent in females than in males; prognosis is better in patients presenting at a younger age. The tumors present as slow-growing, painless masses involving almost every part of the body but predominantly in the trunk and the proximal extremities. Metastatic disease usually occurs earlier than with most other soft tissue sarcomas and is frequently observed at presentation. On the whole, ASPS is poorly circumscribed as it typically grows in an organoid or nest-like arrangement. Lung, brain, and bone are the most common sites of metastasis. In a retrospective study of 11 patients with ASPS (Daigeler *et al*., 2008), time of tumor growth (in the thigh, lower leg, thoracic wall, upper arm, forearm, and foot) before definite diagnoses ranged from 1 month to 20 years. A correlation between the duration of untreated tumor growth and outcome could not be detected. All tumors were located intramuscularly or subfascially and tumor size ranged from 2.9 to 13.5 cm. The tumors grow slowly, with patients remaining asymptomatic for years, even with metastatic disease. However, the ultimate prognosis of this disease is poor (Daigeler *et al*., 2008; Brennan *et al*., 2001; Reichardt *et al*., 2003)

Median survival time following initial diagnosis is 11.4 years, with acturial overall survival (OS) of 74% and 51% at 5 and 10 years, respectively (Lazar *et al*., 2007). There is no effective treatment including radiation and chemotherapy for patients with metastatic ASPS. Given the rarity of the disease, reports regarding overall prognosis are limited. One of the largest series comes from a retrospective review of 74 patients with ASPS treated at MD Anderson Cancer Center (Portera et al. 2001). The majority (n = 48) of these patients presented with advanced, metastatic disease; 33 patients received treatment, of which 26 patients with metastatic disease and 3 patients with localized disease received systematic chemotherapy. Only one of the 33 patients responded to systemic therapy. The 5-year overall survival rate for the 33 patients with metastatic ASPS was 20%. Median survival was 40 months. In a Japanese study of 47 patients with metastatic ASPS, there were no objective responses to systemic intravenous therapy (Ogose et al, Oncology 2003). Based on the review of the literature which revealed lack of observed objective responses to standard chemotherapies and an overall poor prognosis of 20% overall survival at 5 years for patients with advanced metastatic ASPS, we feel that the response rate of 40% targeted in our study is sufficiently high to assess drug activity.

The origin of ASPS remains unclear. The disease is associated with t(X;17)(p11;q25) translocation resulting in ASPL-TFE3 fusion protein, which activates microphthalmia transcription factor (MiT), resulting in over-expression of MET. MET is the receptor for hepatocyte growth factor (HGF), affecting cell survival, adhesion, invasion and migration, and angiogenesis. ASPS is a highly vascular tumor as evidenced by radiologic studies and gene expression studies showing upregulation of genes involved in angiogenesis (Stockwin *et al*., 2009). Results from a gene expression profiling study performed at the NCI identified several transcripts associated with angiogenesis, cell proliferation, metastasis, and myogenic differentiation—the latter suggesting muscle as the cellular origin of this disease (Figure 1). The study collected tumor samples from 7 patients with primary or metastatic ASPS and used microarray analysis and quantitative RT-PCR to compare levels of patient RNA (reverse transcribed to cDNA) with that of a universal reference set from healthy adults (Figure 1) (Stockwin *et al*., 2009). Among the angiogenesis-associated transcripts were c-MET and vascular endothelial growth factor (VEGF), a key angiogenic factor implicated in tumor blood vessel formation and in disease progression in a range of solid tumor malignancies (Hicklin *et al*., 2005).

Correlative studies comparing pre- and post-treatment biopsy specimens from individual patients with ASPS would therefore be expected to provide invaluable data about the pathogenesis of this disease and the mechanism of action of the therapeutic agent. ASPS has been termed a chemo-insensitive tumor, and finding an effective treatment for this rare, slow-growing disease remains a challenge (Daigeler *et al*., 2008). None of the studies with standard chemotherapeutic regimens reports a substantial benefit for this disease. Chemotherapeutic regimens previously assessed include cisplatin, carboplatin, etoposide, vincristine, adriamycin, epiadriamycin, cyclophosphamide, actinomycin, and ifosfamide (Ogose *et al*., 2003; Casanova *et al*., 2000; Kayton *et al*., 2006). Reichardt et al. (2005) reported that chemotherapeutic regimens used for the treatment of other soft tissue sarcomas lack efficacy in ASPS. Benefit was observed only in patients undergoing tumor resection in combination with chemotherapy, radiotherapy, or both, and complete surgical resection has been suggested as the therapy of choice (Anderson *et al*., 2005).

			Microarray		Q-RT-PCR		Patient #						
	Gene ID	Gene Name	Ratio	p value	Ratio	p value	1	2	3	4	5	6	7
Angiogenesis	ANGPTL2	Angiopoietin-like 2	72.9	1.4E-09	152.2	5.1E-04							
	HIF1A	Hypoxia-inducible factor 1, alpha subunit	6.2	8.1E-10	4.2	7.1E-02							
	MDK	Midkine	59.5	1.5E-07	34.5	6.0E-02							
	MET	Met proto-oncogene (HGF Receptor)	10.8	1.0E-06	7.7	4.1E-02							
	PLG	Plasminogen	-49.6	1.1E-24	-110.6	9.7E-03							
	STAB1	Stabilin-1	9.2	6.1E-06	6.4	1.4E-01							
	TIMP2	Metalloproteinase inhibitor 2	14.2	1.3E-05	3.6	3.4E-03							
	VEGF	Vascular endothelial growth factor	3.9	9.3E-06	6.7	1.4E-03							
	VEGFB	Vascular endothelial growth factor B	4.9	5.7E-05	80.8	3.4E-02							
Growth Factors/ Mediators	IGFBP1	Insulin-like growth factor binding protein 1	91.1	1.8E-03	43.6	2.0E-01							
	NTSR2	Neurotensin receptor 2	85.0	1.0E-04	52.2	3.9E-03							
	PCSK1	Proprotein convertase subtilisinkexin 1	24.4	4.7E-05	31.9	1.5E-01							
	PRL	Prolactin	750.5	7.9E-04	155.5	2.7E-03							
DNA/RNA metabolism	IHPK3	Inositol hexakisphosphate kinase 3	34.3	3.2E-09	14.2	2.5E-02							
	PRM1	Protamine 1	-1160.1	2.3E-24	-75.4	6.4E-02							
	PRM2	Protamine 2	-1890.5	1.7E-29	-4.8	2.1E-01							
	UPP1	Uridine phosphorylase	83.9	1.0E-08	86.8	1.1E-04							
Developmental	CPZ	Carboxypeptidase Z	26.2	4.2E-03	88.6	2.3E-04							
	FZD10	Frizzled homolog 10	51.4	1.0E-07	26.6	5.7E-04							
	GPNMB	Glycoprotein Nmb	123.3	2.3E-08	906.9	4.3E-04							
	INHBE	Inhibin beta E	854.3	1.2E-12	126.7	5.7E-04							
	PRKAG2	AMP-activated protein kinase gamma2	66.6	1.1E-07	161.9	1.2E-06							
	PSG9	Pregnancy specific beta-1-glycoprotein 9	82.0	4.4E-02	30.7	1.8E-01							
	BCAT1	Branched-amino-acid aminotransferase	11.6	9.6E-05	7.9	6.7E-02							
	CPXM2	Carboxypeptidase-like protein X2	18.5	3.5E-06	35.3	2.5E-03							
Tissue Restricted	CST2	Cystatin SA	102.8	3.4E-03	710.8	7.9E-02							
	ENO3	Enolase 3 (beta, muscle)	43.2	1.1E-05	49.5	1.0E-04							
	FAP	Human integral membrane serine protease	28.9	9.5E-04	2.8	4.3E-02							
	HES4	Homo sapiens bHLH factor	13.8	1.1E-05	7.0	6.9E-02							
	ITGB1BP3	Muscle-specific beta 1 integrin binding	1238.8	4.3E-13	482.3	5.8E-03							
	KBTBD10	Sarcosin (Kelch-related protein 1)	371.0	6.4E-09	95.0	2.0E-02							
	MYF6	Myogenic factor 6 (Herculin)	300.6	1.2E-10	27.8	6.4E-04							
	NEB	Nebulin	159.4	2.5E-07	11.6	1.2E-01							
	PLOD2	Lysine hydroxylase 2	20.0	1.1E-05	23.7	1.1E-03							
	RAPSN	43kDa postsynaptic protein	12.9	3.6E-07	7.7	2.5E-02							
	SRPX2	Sushi-repeat protein	32.6	3.7E-07	14.9	2.0E-03							
	TRIM63	Muscle-specific RING finger protein 1	726.5	7.9E-11	141.7	6.2E-02							
Drug Resistance	ABCB5	ATP-binding cassette sub-family B5	227.4	1.1E-02	8.7	1.2E-01							
	ABCC9	ATP-binding cassette, sub-family C9	20.9	3.4E-03	24.5	2.1E-02							
	NAT8	N-acetyltransferase 8	-917.7	7.7E-23	-4.1	1.9E-03							
Cell Cycle	ABP1	Amiloride binding protein 1	-269.5	1.7E-18	-13.0	5.8E-05							
	CCND1	Cyclin D1	13.6	8.4E-06	86.1	8.3E-03							
	UMOD	Uromodulin	-2235.2	1.6E-22	-43.2	2.7E-03							
Steroid Biosynthesis	CYP17A1	Steroid 17-alpha-hydroxylase	33.2	2.2E-02	454.3	7.1E-03							
	STS	Steroid sulfatase (microsomal)	62.4	2.6E-05	68.9	2.6E-03							
Metastasis	ADAM9	Disintegrin metalloproteinase domain 9	9.0	5.2E-04	33.6	1.2E-03							
	CHI3L2	Chitinase	34.6	2.3E-02	129.7	2.9E-02							
	CTSK	Cathepsin K	19.2	1.0E-05	368.3	8.2E-05							
	ECM1	Extracellular matrix protein 1	19.6	1.1E-04	198.6	1.1E-01							
	POSTN	Periostin	71.0	8.4E-04	138.7	2.9E-02							
Apoptosis	BIRC7	Livin inhibitor-of-apoptosis	32.6	4.5E-04	79.1	6.0E-03							
	CASP4	Caspase-4	7.9	4.3E-08	27.3	1.3E-03							
Adhesion Molecules	CTNND2	Catenin delta-2	-43.7	1.7E-15	-3.6	5.1E-02							
	SCARB1	Scavenger receptor class B, member 1	31.9	4.6E-09	141.4	1.6E-03							
Transcription Factors	BHLHB3	BHLH protein DEC2	9.8	3.9E-05	49.5	5.2E-04							
	RFX4	Transcription factor NYD-sp10	-282.7	1.5E-20	-14.5	5.2E-05							
Unknowns	C20orf26	Chromosome 20 open reading frame 26	146.8	7.9E-05	36.3	1.1E-01							
	KIAA0350	Hypothetical protein LOC23274	182.9	8.0E-08	56.0	5.1E-04							

Figure 1: Heatmap of a subset of aberrantly expressed genes from 7 patients with ASPS identified by microarray/qRT-PCR analysis (Stockwin *et al*., 2009).

Interferon alpha-2b treatment of patients with ASPS was shown to be of some benefit (Bisogno *et al*., 2005; Kuriyama *et al*., 2001; Roozendaal *et al*., 2003), but the most promising systemic treatment was reported in 2006, when a case report indicated tumor regression in a patient with disseminated ASPS during antiangiogenic treatment with bevacizumab, an antibody against VEGF. It was concluded that inhibition of the VEGF signaling pathway alone or in combination

with drugs targeting other proangiogenic factors could be an important new treatment option for patients with ASPS (Azizi *et al*., 2006).

Approximately 10 clinical trials are currently recruiting patients with ASPS [http://clinicaltrials.gov]. These include trials with vorinostat and bortezomib; oral gamma-secretase inhibitor RO4929097 with or without oral hedgehog antagonist GDC-0449; radiation therapy; combination chemotherapy with doxorubicin and ifosfamide, and/or surgery; dasatinib (an oral dual BCR/ABL and tyrosine kinase inhibitor); and various combination chemotherapy, surgical, and radiotherapy techniques. Common inclusion criteria for these studies of ASPS include progressive, unresectable, recurrent or metastatic histologically confirmed disease that has either not been treated or is nonresponsive to standard therapies.

2.2 Cediranib (AZD2171)

Cediranib (AZD2171, Recentin™; 4-[(4-fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy) quinazoline maleate; AZD2171 maleate) is a member of an emerging class of novel orally-administered small molecule VEGF receptor tyrosine kinase (TK) inhibitors with anti-angiogenic properties (Hennequin *et al*., 1999; Wedge *et al.,* 2005).

Mechanism of Action
VEGF is a key angiogenic factor, and has been implicated in tumor blood vessel formation and in disease progression in a range of solid tumor malignancies (Hicklin and Ellis, 2005). Two high-affinity VEGF transmembrane receptors (VEGFRs) with associated TK activity have been identified on human vascular endothelium, VEGFR-1 (also known as fms-like tyrosine kinase 1 or Flt-1) and VEGFR-2 (also known as kinase insert domain-containing receptor or KDR) (Ferrara *et al*., 2003). VEGFR-1 and VEGFR-2 signaling help mediate tumor progression. Cediranib has been developed as a potent inhibitor of VEGFR-1 and VEGFR-2 (Wedge *et al*., 2005). Cediranib also has activity against VEGFR-3 and c-Kit (Jurgensmeier *et al*., 2005). Cediranib is expected, with chronic oral dosing, to inhibit VEGF-driven angiogenesis and as a result prevent the progression and metastasis of solid tumors, and may have broad-spectrum clinical utility.

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 0.75-6 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 efficacy studies (Drevs *et al.*, 2004). In experiments incorporating a vehicle control, cediranib (at a dose of

6.3 mg/kg/day PO) reduced primary tumor growth, metastasis, and microvessel density more potently than any other previously studied VEGF RTK inhibitor reported in the literature.

Using a transgenic mouse model in which multiple mammary tumors spontaneously develop after two pregnancies, investigators studied the temporal effects of cediranib administration (Klinowska *et al.*, 2004). When dosed with cediranib (0.75-6 mg/kg/day PO) at the time early lesions start to develop, the number of tumor foci was not affected, but their growth was inhibited. When tumors were well established before cediranib was given (at doses of 3 and 6 mg/kg/day), dose-dependent growth inhibition occurred as well as tumor regression.

Further details of the non-clinical efficacy of cediranib can be found in Section 4.1 of the Investigator's Brochure (2009).

Nonclinical Pharmacology and Toxicology
Nonclinical pharmacology and toxicology company-sponsored studies have been conducted in rats, dogs, and cynomolgus monkeys. In rats and dogs, oral bioavailability is high, but absorption is relatively slow, with peak plasma concentration (C_{max}) of the agent seen 4-6 hours after oral 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 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 0.05-2.5 mg/kg.

Protein binding of cediranib (90-95%) was relatively high across all species examined and was independent of concentration (range: 0.03-10 mcg/mL) and gender. Cediranib was approximately 95% bound to human plasma proteins, with human serum albumin and 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 40-60% reduction in CYP1A activity at the 5 mg/kg dose level. This may indicate suppression of CYP1A or be related to decreased liver weight. This change was not considered significant. 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; these concentrations were in excess of those found in current clinical studies and would therefore not be expected to cause clinically significant drug interactions through inhibition of P450-mediated metabolism of co-administered agents. For CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1, the IC_{50} values were outside the concentration range of cediranib examined.

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 (2009), respectively.

Clinical Pharmacology
Preliminary pharmacokinetics (PK) information indicates a time to maximum serum concentration (T_{max}) of 2 hours (range, 2-6 hours), a maximum serum concentration (C_{max}) of 107.8 ± 29.8 ng/mL, and a distribution half-life ($t_{1/2}$) of 12.1 ± 2.2 hours (Sridhar *et al*., 2008).

In vitro studies suggested that CYP enzymes were not significantly involved in the production of the principle human metabolites of cediranib, therefore co-administration of known inhibitors or inducers of hepatic CYP enzymes would not be expected to have significant effects on the clearance of cediranib. However, since potent inhibitors or inducers of CYP enzymes can also affect drug disposition by interaction with transporter proteins and phase II metabolism, 2 clinical studies were conducted to investigate the PK of cediranib when co-administered with a potent inhibitor (ketoconazole,) and a potent inducer (rifampicin) of CYP enzymes. Co-administration of ketoconazole 400 mg modestly increased the AUC_{ss} and $C_{ss,max}$ of cediranib 20 mg. Co-administration of rifampicin 600 mg resulted in a decrease in the AUCss and $C_{ss,max}$ of cediranib 45 mg. In both studies, due to the relatively small magnitude of change in AUCss and $C_{ss,max}$ and the known PK variability of cediranib, the effect was not considered to be clinically significant (Investigator's Brochure, 2009).

Preliminary information on blood biomarkers in glioblastoma patients indicates that plasma VEGF, placental growth factor (PIGF), and stromal cell-derived factor-1α (SDF1α) were increased after treatment, and plasma PIGF and VEGF decreased upon cediranib discontinuation. Plasma basic fibroblast growth factor (bFGF) and SDF1α and viable circulating endothelial cells (CECs) increased when tumors escaped treatment with cediranib (Batchelor *et al*., 2008).

Additional information on the relationship between clinical outcome and biomarkers has been reported for a DCTD-sponsored trial (Sorensen *et al*., 2009). Changes in vascular permeability/flow as measured by magnetic resonance imaging (MRI) methods (K^{trans}), microvessel volume, and circulating collagen IV levels were determined. Of the 30 patients in the trial, all three parameters were reliably measured in 28. A greater reduction in K^{trans} after one

dose of cediranib was seen in patients with increased progression-free survival (PFS) (*P*=0.0015) and overall survival (OS) (*P*=0.0039). A greater increase in the calculated blood volume (CBV) of tumor microvessels after one dose of cediranib was seen in glioblastoma patients with extended OS (*P*=0.0056). A greater increase in collagen IV levels in plasma was detected in patients with extended PFS (*P*=0.0010). Peripheral blood was evaluated serially for VEGF concentration and CECs in another trial (Ramalingam *et al*., 2008). A stark increase in CECs was noted at progression in several patients

Adverse Events and Efficacy
Hypertension is an expected pharmacologic effect of agents that inhibit VEGF, and is one of the most common adverse events (AEs) reported in trials of cediranib. Dose-related increases in thyroid stimulating hormone (TSH) and decreases in total thyroxine have been observed at doses of 30 mg and above, and are most marked at 60 mg. The most frequently reported AEs on company-sponsored trials were fatigue, diarrhea, nausea, vomiting, hoarseness, hand-foot syndrome, and hypertension (Investigator's Brochure, 2009). The recommended dose for monotherapy is 30 mg/day; the recommended dose in combination with chemotherapy agents is 20 mg/day, although exceptions to these doses may be appropriate in other studies, depending on age, patient population, tumor type, or agent(s) given in combination with cediranib.

Complete responses (CRs) and partial responses (PRs) have been reported in clinical trials of cediranib in solid tumors such as non-small cell lung cancer (NSCLC) (Gadgeel *et al*., 2009), renal cell carcinoma (RCC) (Sridhar *et al*., 2008), prostate (Karakunnel *et al*., 2009), mesothelioma (Garland *et al*., 2009), and gynecologic tumors (Hirte *et al*., 2008; Matulonis *et al*., 2009).

Clinical Experience
AstraZeneca has sponsored a total of 15 phase 1 studies of cediranib (single-agent or in combination with gefitinib, either FOLFOX, irinotecan [±cetuximab], pemetrexed or docetaxel, etoposide/cisplatin, or lomustine), 8 phase 2 studies (single-agent, or in combination with fulvestran, FOLFOX, or paclitaxel/carboplatin), one phase 2/3 study (cediranib plus bevacizumab), and two phase 3 studies (cediranib plus FOLFOX or XELOX and cediranib plus lomustine). Details of the studies, responses, and safety assessments are summarized in the Investigator's Brochure (2009).

Cediranib has been administered to patients in 23 DCTD, NCI-sponsored clinical trials.

The MTD for cediranib in combination with temozolomide and radiation was established at 30 mg/day. Cediranib was then administered at 45 mg/day in a post-radiation setting, and in addition to the expected AEs of hypertension, fatigue, and palmar/plantar erythema, one patient discontinued due to grade 3 transaminase elevation and one patient required dose reduction to 15 mg/day due to proteinuria (Chi *et al*., 2009)

Among 31 patients in a phase 2 trial of cediranib in recurrent glioblastoma, radiographic PRs were reported in 16 (Batchelor *et al*., 2008). Progression-free survival (PFS) was 117 days, and overall survival (OS) was 221 days. Additionally, cediranib alleviated brain edema, a major

cause of morbidity in glioblastoma patients. Dose-limiting toxicities (DLTs) were observed in 9 of the 16 patients with hypertension; fatigue and diarrhea were seen most often.

An interim analysis of 19 of 28 patients accrued to a study of cediranib in hepatocellular carcinoma (HCC) reported that 16 of the 19 developed grade 3 AEs (Alberts *et al*., 2007). Fatigue, hypertension, and anorexia accounted for the majority of the AEs.

Response information for 45 of 46 patients on a trial of cediranib in malignant pleural mesothelioma reported tumor response by RECIST in 4/45 patients; 2 patients with bulky disease had 56% and 91% tumor shrinkage, respectively; 15/45 had stable disease (SD); 21/45 had progressive disease (PD); and one patient suffered early death (Garland *et al*., 2009). For 46 patients, median PFS was estimated at 3 months, median OS at 10 months. Overall disease control rate (complete response [CR]/partial response [PR]/stable disease [SD]) was 42% by RECIST. Eight grade 4 events were reported: cognitive disturbance, colitis, confusion, ileal perforation, hypertension, hyponatremia, hypotension, and renal failure.

Among 47 evaluable patients receiving cediranib in a trial in ovarian, primary peritoneal serous, or fallopian tube cancer, the clinical benefit rate was 30%; eight patients had a PR and six had SD; there were no CRs (Matulonis *et al*., 2009). Median PFS was 5.2 months, and median OS had not been reached after a median follow-up time of 10.7 months. Grade 4 AEs included CNS hemorrhage, lipase, and hypertriglyceridemia/hypercholesterolemia/elevated lipase, and dehydration/elevated creatinine. Grade 3 AEs include hypertension, fatigue, and diarrhea. Hypertension occurred in 87% of the patients by the end of the study; in 43%, it was grade ≥3 (Robinson *et al*., 2010). Grade 2 hypothyroidism occurred in 43% of patients.

Preliminary information from 60 patients in a phase 2 trial of cediranib in persistent ovarian, peritoneal, or fallopian tube cancer has been reported (Hirte *et al*., 2008). Patients were divided into those whose disease was found to be platinum-resistant and those whose disease was platinum-sensitive in a prior therapy regimen. Response and prolonged SD rate was 41% for platinum-sensitive and 29% for platinum-resistant patients, respectively. In the platinum-sensitive group, there were two confirmed PRs and one unconfirmed PR, while one unconfirmed PR was observed in the platinum-resistant arm. Median time to progression (TTP) and median survival for all patients was 4.1 months and 11.9 months, respectively, with no significant differences between the platinum-sensitive and -resistant groups. The most frequent AEs were fatigue, diarrhea, hypertension, and anorexia, while hypertension and fatigue were the most frequent grade 3 or higher AEs. Sixteen patients required dose reduction to 30 mg and 20 mg.

Information on 34 patients in a trial of cediranib in metastatic androgen-independent prostate cancer has been reported (Karakunnel *et al*., 2009). There have been 13 of 23 evaluable patients with tumor shrinkage (4 have met the criteria for PR). Decreases in lymph node metastases as well as in lung, liver, and bone lesions have occurred. Grade 3 AEs included vomiting, prolonged QTc interval, muscle weakness, weight loss, dehydration, fatigue, hypoxia, renal failure, transaminitis, and anorexia.

Thirty-two of 43 patients enrolled in a trial of cediranib in renal cell carcinoma (RCC) are evaluable for response (Sridhar *et al*., 2008). PRs were observed in 12 patients, SD in 15, and

PD in 5. Median PFS was 8.7 months and the 6-month progression-free proportion was 63%. Treatment-related grade 3 or higher AEs included hypertension, fatigue, joint pain, abdominal pain, and dyspnea.

Cediranib was administered in a phase 2 trial in small cell lung cancer (SCLC), in which one unconfirmed PR and eight SD were noted (Ramalingam *et al*., 2008). Salient AEs were fatigue (four grade 3, two grade 4), and grade 3 diarrhea, skin rash, proteinuria, transaminitis, muscle weakness, and hypertension. However, the original 45 mg/day dose was not tolerable in the patient population, and the modest activity seen at 30 mg/day did not support the use of cediranib as monotherapy for SCLC.

A combination trial of cediranib plus docetaxel, doxorubicin, and cyclophosphamide in advanced breast cancer accrued only two patients, and was closed due to systolic dysfunction that occurred with concurrent cediranib and doxorubicin (Denduluri *et al*., 2007).

Another combination trial of cediranib plus pemetrexed in NSCLC divided patients into two arms—those who had not received bevacizumab in prior chemotherapy regimens (Cohort A), and those who had (Cohort B) (Gadgeel *et al*., 2009). The confirmed response rate was 16% (10% Cohort A, 25% Cohort B), and the disease control rate (CR/PR/SD) was 71% (74% Cohort A, 67% Cohort B). Grade 3/4 AEs included neutropenia, febrile neutropenia, fatigue, diarrhea, hypertension, anorexia, cardiac ischemia, bronchopleural fistula, and esophagitis. Of the 17 patients who received cediranib for 4 cycles, 71% required dose reduction from 30 mg/day, and of the 18 patients who received pemetrexed for 4 cycles, 22% required dose reduction. Additional information on clinical trials conducted with cediranib is summarized in Lindsay *et al*. (2009).

Results from Phase III trials with cediranib were presented in 2010:
Horizon III summary (Schmoll *et al.*, 2010): Together with the HORIZON II data showing a significant improvement in PFS (HR=0.84) with a comparable hazard ratio to the NO16966 FOLFOX bevacizumab trial (HR=0.83), HORIZON III data suggest that the oral VEGFR inhibitor cediranib has clinical activity in mCRC with no significant difference in efficacy outcomes compared to bevacizumab. However, the toxicity burden is greater than bevacizumab, and this would limit its use in routine clinical practice.

Horizon II summary (Hoff *et al.*, 2010): Cediranib is the first small molecule to show clinical activity against colorectal cancer. Cediranib met the co-primary endpoint of PFS (HR=0.84; P=0.0121); however, no OS benefit was observed (HR=0.94). There was no significant difference in RR, DoR, or rate of liver resection. The AEs associated with cediranib were consistent with previous studies and generally consistent across chemotherapy regimens. The incidence of grade ≥3 AEs was higher in the cediranib arm. Grade ≥3 diarrhea, hypertension, neutropenia and thrombocytopenia were experienced by >5% more patients in the cediranib arm. The AEs associated with cediranib were manageable, but resulted in reduced chemotherapy delivery.

REGAL summary (Batchelor *et al.*, 2010): Cediranib showed evidence of clinical activity in recurrent glioblastoma. However, the study did not meet the primary endpoint on PFS for either

cediranib alone or in combination with lomustine and showed no benefit on OS versus lomustine alone. Effects were observed in some secondary endpoints: Early effects seen (as demonstrated by change in contrast enhancing area and response rate) that were not maintained; Statistically significant difference between cediranib 30 mg monotherapy and lomustine in change in steroid usage; significant difference in favor of the combination arm versus lomustine alone on TDNS and change in steroid use. The adverse event profile was broadly consistent with previous trials. Cediranib dose intensity was well maintained in both arms; however, there were more lomustine dose reductions in the combination arm compared with lomustine alone.

Table 1: Summary of Pertinent Clinical Trials With Cediranib (Lindsay *et al*., 2009)

Study	Clinical phase	Cancer type	Dose(s) used	Significant toxicities	Efficacy
Drevs *et al.* (2007)	Phase I	Solid tumors	RP2D = 45 mg once-daily	21/83 DLTs including hypertension (most commonly), fatigue and nausea	2/83 partial responses 22/83 stable disease
Laurie *et al.* (2008)	Phase I	Lung	RP2D = 30 mg (with carboplatin + paclitaxel)	Grade III–IV: hypertension (35%), fatigue (60%), anorexia (35%), diarrhea (30%), mucositis (20%)	9/20 partial responses 11/20 stable disease
Goss *et al.* (2009)	Phase I	Lung	RP2D = 30 mg (with cisplatin and gemcitabine)	8 /12 patients had grade III toxicities (hypertension, fatigue, diarrhea, voice changes); 2 had grade IV toxicities (1 reversible CNS ischemia, 1 fatigue)	5/9 partial responses 4/9 stable disease
Mayer *et al.* (2007)	Phase II	Breast	45 mg once-daily	Grade III–IV: hypertension (42%), diarrhea (19%), fatigue (19%), mucositis (12%)	2/20 partial responses 10/20 stable disease
Ryan *et al.* (2007)	Phase I	Prostate	RP2D = 20 mg once-daily	3/4 patients with DLTs of hypertension and proximal muscle weakness at 30 mg once-daily	Post-therapy PSA decline persisted for >17 months in two patients. One radiological response post-therapy
Karakunnel *et al.* (2008)	Phase II	Prostate	20 mg once-daily	4/18 grade III toxicities: vomiting, myalgia, prolonged QTc complexes	2/18 partial responses
Sridhar *et al*. (2008)	Phase II	Renal	45 mg once-daily	36 grade III–IV toxicities including hypertension, fatigue and arthralgia	12/32 partial responses 15/32 stable disease
Matulonis *et al.* (2008)	Phase II	Ovarian	45 mg → 30 mg once-daily	13/28 grade III toxicities including hypertension, fatigue and diarrhea. One grade IV CNS hemorrhage	5/28 partial responses 3/28 stable diseases
Hirte *et al.* (2008)	Phase II	Ovarian	45 mg → 30 mg once-daily	Most frequent grade III–IV toxicities were hypertension (20/60) and fatigue (12/60)	Response and prolonged stable disease rate was 41% and 29% for platinum-sensitive and platinum-resistant patients, respectively

Study	Clinical phase	Cancer type	Dose(s) used	Significant toxicities	Efficacy
Cunningham *et al.* (2008)	Phase II	Colorectal	20 mg or 30 mg once-daily (with FOLFOX)	↑ hypertension, asthenia and thrombocytopenia compared with bevacizumab + FOLFOX	Progression-free survival slightly longer in bevacizumab arm

Starting Dose
Although 45 mg was the initial recommended Phase II dose based on results from Study 2171IL/0001, subsequent studies have indicated that many patients require a dose reduction (Lindsay *et al*., 2009). For example, the starting dose was reduced to 30 mg in two monotherapy Phase II trials in ovarian cancer due to toxicities observed at the 45-mg dose level (Hirte *et al*., 2008; Matulonis *et al*., 2008). In one of these trials, 28 patients received cediranib, and Grade ≥3 AEs included hypertension, fatigue, diarrhea, vomiting, hyponatremia, oral cavity pain, nausea, constipation, abdominal pain, headache, and hypothyroidism; Grade 4 toxicities included CNS hemorrhage, lipase, and hypertriglyceridemia (Matulonis *et al*., 2008). In the other trial, hypertension and fatigue were the most frequent Grade ≥3 AEs (Hirte *et al*., 2008). Similarly, in a Phase II study of cediranib in recurrent small cell lung cancer, 7 of the first 12 patients enrolled were unable to complete the first cycle at 45 mg due to AEs, and the starting dose was subsequently reduced to 30 mg). Salient Grade 3 toxicities were fatigue, proteinuria, diarrhea, skin rash, transaminitis, muscle weakness, and hypertension. Two patients had Grade 4 fatigue.

In summary, a higher incidence of toxicities has been observed in several studies at 45 mg, and subsequently 30 mg has been widely used as a single-agent Phase II dose. In a randomized study evaluating both the 30 and 45 mg doses of cediranib with or without antihypertension prophylaxis in patients with advanced solid tumors, the overall response rate was similar across treatment groups with evidence of antitumor activity at both the 30-mg and 40-mg dose levels (N=125; Investigator's Brochure, 2009). Cediranib doses as low as 20 mg daily in patients with advanced prostate cancer resulted in plasma concentrations above the concentration required to inhibit endothelial cell growth (Ryan *et al*., 2007).

Clinical Efficacy of Cediranib in ASPS
The clinical efficacy data which form the basis for studying cediranib in ASPS are primarily from Phase I and II trials sponsored by Astra Zeneca at the Royal Marsden Hospital, London, UK and the Christie Hospital, Manchester, UK. Efficacy and tolerability data were collected for 7 patients with ASPS (ages 26–49 years) treated with cediranib; one patient was treated in a Phase II randomized trial of cediranib with or without prophylactic antihypertensive therapy, and 6 patients were treated in a Phase II study in patients with imatinib-refractory gastrointestinal stromal tumours (GIST) or other soft tissue sarcoma (Gardner *et al.*, 2009). Cediranib was administered orally once daily at an initial dose of 45 mg/day. Four patients had confirmed partial responses that lasted for 241, 247, 365, and 633 days, respectively. Two other patients had disease stabilization lasting 57 and 449 days, respectively. The most frequently reported adverse events in patients with ASPS were similar to those reported in the other studies (Drevs *et al*., 2007; Langenberg *et al*., 2009): fatigue, diarrhea, stomatitis, headache, and hypertension (Gardner *et al*., 2009). These data demonstrated an exciting activity profile for cediranib that supported further investigation in patients with ASPS (Figure 2).

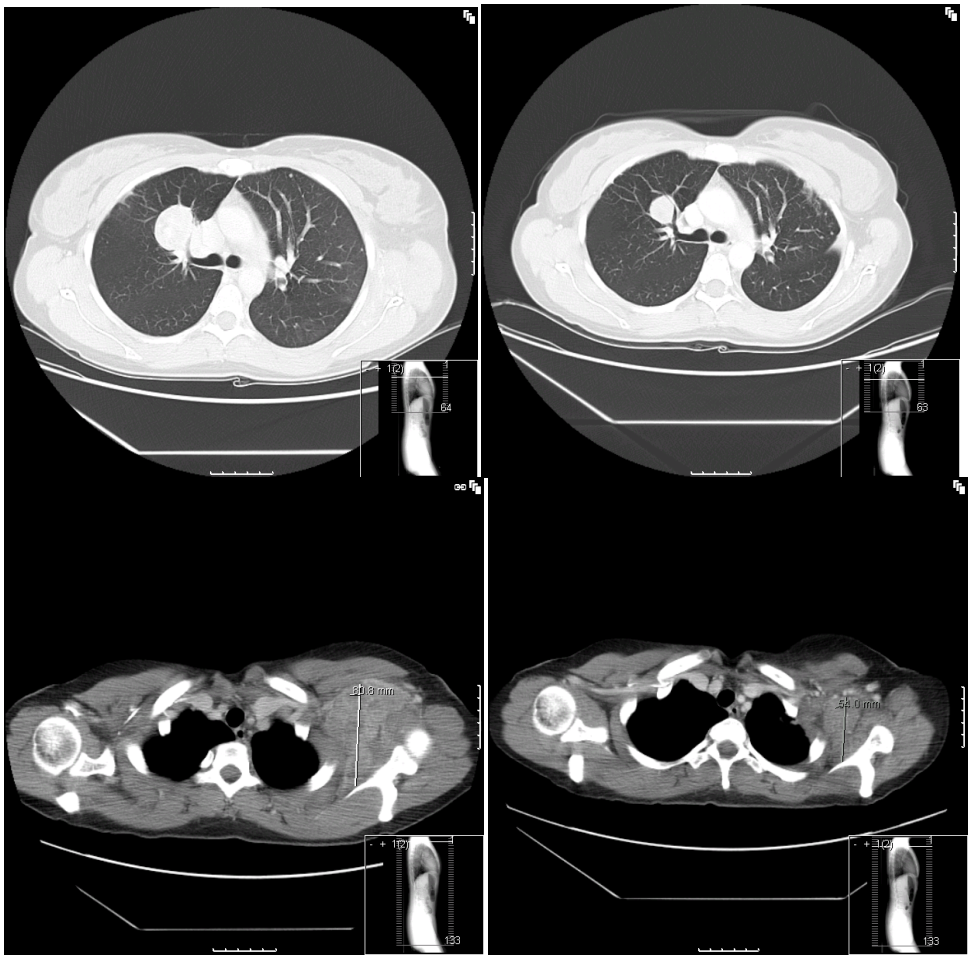


Figure 2: Pre- and post-treatment CT scans from a young woman with ASPS in the axilla and lungs treated with cediranib from August 2006 to June 2008.

Phase II Single-Center Study of Cediranib at the NCI

The NCI opened a single-arm Phase II trial to determine the response rate (PR + CR) of cediranib in patients with advanced ASPS (09-C-0192) in 2009. The trial is designed to rule out 5% clinical response rate (PR+CR; p0 = 0.05) in favor of a modestly high response rate of 25% (p1= 0.25). Patients are treated with 30 mg cediranib by mouth for 28 days in 28-day cycles. The target accrual was initially 24 patients but has since been expanded to a total of 54 patients. We have accrued 36 patients as of January 2011; 28 of these patients are evaluable for response (i.e., have completed at least 2 cycles of therapy). We have observed 12 PR and 4 MR (defined as > 20% reduction in the sum of the longest dimensions of the target lesions). Adverse events have been manageable; CTCAE v. 3.0 Grade 2 and 3, related to study medication: hypertension, elevated transaminases, hyperbilirubinemia, neutropenia, anorexia, tumor pain, hypothyroidism, weight loss, mucositis, confusion, diarrhea, fatigue, vomiting, and proteinuria.

Safety Profile
As of January 2011, 895 patients on DCTD, NCI-sponsored clinical trials of cediranib had been evaluated for AEs. The most common grade 3/4 AEs were hypertension, fatigue, anorexia, diarrhea, and metabolic (ASL/SGPT and AST/SGOT). Please refer to Section 7.1.1 for a comprehensive list of potential AEs associated with cediranib.

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

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

In a phase 2 study of cediranib in patients with solid tumors, patients (n=126) were assigned to cediranib dose groups of either 45 or 30 mg/day with or without antihypertensive prophylaxis (Langenberg *et al*., 2009). Severe hypertension occurred in one patient receiving prophylaxis *versus* 18 in the nonprophylaxis groups. Antihypertensive prophylaxis did not result in fewer dose reductions or interruptions. Increases in blood pressure, including moderate and severe readings of hypertension, were seen in all groups and successfully managed.

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

As described above (Starting Dose), the 30 mg cediranib dose has generally been better tolerated than the 45 mg dose.

2.3 Sunitinib Malate

Sunitinib malate (sunitinib; SU11248; SU011248; Sutent®) is an oral, multi-targeted, small molecule inhibitor of the receptor tyrosine kinases (RTKs) involved in tumor proliferation and angiogenesis, including vascular endothelial growth factor receptor-1 (VEGFR-1), -2, and -3, platelet-derived growth factor receptor (PDGFR) -α and -β, stem cell factor receptor (KIT), the tyrosine kinase (TK) receptor encoded by the *ret* proto-oncogene (RET; rearranged during

transfection), fms-like tyrosine kinase 3 (Flt3), basic fibroblast growth factor (bFGF) and colony-stimulating factor (CSF)-1R (O'Farrell *et al.*, 2003a; Chow and Eckhardt, 2007; Faivre *et al.,* 2007; Gan *et al*., 2009; Mashkani *et al.*, 2010). Sunitinib selectively and potently inhibits the class III and class V split-domain RTKs (Mendel *et al*., 2003).

Sunitinib shows significant antitumor and anti-angiogenic activity in a number of human tumor xenograft and angiogenesis models in mice as well as in phase 1 and 2 studies in patients with a variety of tumor types (Gan *et al.,* 2009; Mena *et al.,* 2010). As of June 2008, a total of 8932 subjects with solid malignant tumors have received sunitinib, including patients with renal cell carcinoma (RCC) and those with gastrointestinal stromal tumors (GIST) (Investigator's Brochure, 2009). In phase 2 studies in cytokine-refractory metastatic RCC, sunitinib produced objective responses in 40% of patients with a median time-to-tumor-progression (TTP) of 8.7 months (Motzer *et al.,* 2006). In phase 3 studies of patients with imatinib-resistant GIST, sunitinib was highly superior to placebo ($p<0.0001$) with respect to median TTP (27.3 weeks vs. 6.4 weeks), progression-free survival (PFS), and overall survival (OS) (Demetri *et al.,* 2006). Sunitinib was granted regular approval on January 26, 2006 by Food and Drug Administration (FDA) for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerant to imatinib mesylate and accelerated approval for advanced renal cell carcinoma (RCC) (Goodman *et al.,* 2007; Izzedine *et al*., 2007; Rock *et al*., 2007), which was changed to regular approval on February 2, 2007.

Mechanism of Action

Tumor VEGF expression has been associated clinically with disease prognosis in many different types of malignancies. VEGF expression is increased by diverse stimuli including proto-oncogene activation and hypoxia, with the hypoxic state frequently arising in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature thereby, potentially contributing to tumor progression. A leaky tumor endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumor cell migration and intravasation during metastasis. Two high-affinity receptors for VEGF with associated TK activity have been identified on human vascular endothelium; VEGFR-1/Flt-1 and VEGFR-2/kinase insert domain-containing receptor (KDR). 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.

In addition to VEGF receptor signaling, increasing evidence implicates PDGFR signaling in tumor angiogenesis. Recent nonclinical evidence suggests that inhibition of PDGFR signaling augments the antitumor and anti-angiogenic effects of VEGFR inhibitors. In addition, PDGF signaling is implicated in the autocrine growth of tumor cells and in the recruitment and regulation of tumor fibroblasts.

Upon chronic oral dosing, sunitinib is expected to inhibit PDGF- and VEGF-driven angiogenesis and as a consequence, limit solid tumor growth. Because angiogenesis is necessary for the growth and metastasis of solid tumors, and VEGF is believed to have a pivotal role in this process, sunitinib treatment may have broad-spectrum clinical utility (Chow and Eckhardt, 2007; Gan *et al*., 2009). Sunitinib also exerts direct antitumor activity on cells that express target

RTKs associated with tumor cell proliferation, such as KIT, PDGFR, and RET. The clinical activity of sunitinib in patients with advanced GIST is an example of this antitumor effect.

Clinical Experience
As of June 2008, 9204 subjects had received at least one dose of sunitinib in 77 completed or ongoing clinical studies, with 8986 subjects having received multiple doses of the agent (Investigator's Brochure, 2009). In phase 1 studies, sunitinib demonstrated single-agent activity in patients with RCC, GIST, non-GIST sarcomas, non-small cell lung cancer (NSCLC), colorectal cancer, neuroendocrine tumors (NET), melanoma, prostate cancer, and thyroid cancer. Sunitinib has also been studied in the phase 1 setting in patients with acute myeloid leukemia (AML). Pivotal trials of sunitinib in imatinib-resistant GIST (a placebo-controlled phase 3 trial), and metastatic RCC (MRCC) (single-arm, non-randomized, multicenter, open-label trial) and supporting trials in each disease were completed and submitted in support of the New Drug Application (NDA). In addition, there are several ongoing company-sponsored single agent and combination clinical trials for a variety of other indications.

Phase 1 Experience
In an early phase 1 study designed to investigate dosing regimen and scheduling (in human subjects, the results of clinical pharmacology studies demonstrate that C_{max} and AUC increased in a proportional manner after single doses of 50 to 350 mg as well as after multiple doses of 25-100 mg), 41 patients with a variety of advanced solid tumors received sunitinib administered on a schedule of 2 weeks of treatment followed by 2 weeks off (2/2 schedule) or 4 weeks on with 2 weeks off (4/2 schedule) (Rosen *et al*., 2003). Doses evaluated on the 2/2 schedule (n=23) included 50 mg every other day (n=3), 50 mg daily (n=15), or 75 mg daily (n=5); the 18 patients enrolled in the 4/2 schedule received 25 mg daily (n=3) or 50 mg daily (n=15). The most frequent adverse events (AEs) were constitutional (fatigue/asthenia), gastrointestinal (nausea, vomiting, diarrhea) and hematologic (neutropenia, thrombocytopenia). Most of the AEs were grade 1 or 2, although at 75 mg daily, grade 3 and 4 fatigue/asthenia were dose limiting but readily reversible on discontinuation of treatment. There were 4 partial responses (PRs) assessed by RECIST and 22 patients with stable disease (SD) among the 41 patients.

A phase 1 dose-escalation study in 28 patients with advanced tumors evaluated sunitinib doses of 30 mg/m^2 every other day, and doses of 30, 42, or 59 mg/m^2 daily on the 4/2 schedule (Faivre *et al*., 2006). Grade 3 fatigue and hypertension were dose limiting at 59 mg/m^2 as well as grade 2 bullous skin toxicity, and the MTD was defined as 42 mg/m^2 daily. Based on these and other reversible AEs in the 12 patients treated at the MTD, the recommended phase 2 dose on the 4/2 schedule was determined to be 50 mg/day. Responses determined by RECIST were seen in 6 of 23 evaluable patients: 3 in RCC, 1 in NET, 1 in GIST, and 1 in adenocarcinoma of unknown primary. Tumor responses in patients treated at higher doses were often associated with reduced intratumoral vascularization and central tumor necrosis, leading to organ perforation in one patient and fistula in another. These observations suggest the possible necessity for careful tumor density monitoring to detect early evidence of necrosis.

Two phase 1 studies have been conducted in AML, the first with the primary endpoint of evaluation of the inhibition of FLT3 phosphorylation (O'Farrell *et al.*, 2003b) and the second designed as a conventional dose-escalation study (Fiedler *et al*., 2005). O'Farrell and colleagues

studied FLT3 phosphorylation in 29 AML patients who received a single dose of sunitinib at doses ranging from 50-350 mg. Over 50% of patients showed strong inhibition of Flt3 phosphorylation at doses of 200 mg and higher. As anticipated from nonclinical data, patients with FLT3 internal tandem duplication (ITD) mutations were more sensitive than those with wild-type Flt3 (FLT3-WT) as shown by 100% inhibition in FLT3-ITD compared to 50% in FLT3-WT. This study also gave evidence of downstream signal inhibition (STAT5 and ERK pathways), with STAT5 levels reduced primarily in FLT3-ITD patients while ERK inhibition occurred in the majority of patients independently of FLT3 inhibition. The dose-escalation study enrolled 15 patients with refractory or resistant AML who were treated with sunitinib on either the 4/2 or 4/1 schedule at a starting dose of 50 mg/day (Fiedler *et al*., 2005). Dose-limiting AEs (grade 4 fatigue and hypertension) occurred in both patients treated at 75 mg/day, and one of these patients (who had received prior mitoxantrone) developed cardiac failure. The 75 mg dose level was therefore terminated and 50 mg/day was considered to be the MTD. All four patients with FLT3 mutations had morphologic or partial responses compared to 2 of 10 evaluable patients with wild-type FLT3. Responses, although longer in patients with mutated FLT3, were of short duration.

Preliminary results from phase 1 studies exploring the combination of sunitinib with chemotherapeutic agents like capecitabine (Sweeney *et al.*, 2007; Chiorean *et al.*, 2008; Royce *et al.*, 2008), pemetrexed (Chow *et al.*, 2008), docetaxel (Traynor *et al.*, 2008), gemcitabine (Brell *et al*., 2008; Michaelson *et al.,* 2008), FOLFOX (Leong *et al.,* 2007), FOLFIRI (Starling *et al.,* 2008), carboplatin/paclitaxel (Heath *et al.,* 2008), and metronomic cyclophosphamide/methotrexate (Rugo *et al*., 2008) in patients with various solid tumors have been presented. The MTD of sunitinib on the 4/2 schedule with docetaxel (60 mg/m^2) was 25 mg daily; with capecitabine (1000 mg/m^2), it was 37.5 mg daily. The MTD of sunitinib on the 2/1 schedule with docetaxel (75 mg/m^2) was 37.5 mg daily and with capecitabine (1000 mg/m^2) was 50 mg daily. The MTD for sunitinib as continuous daily dosing (CDD) with capecitabine (1000 mg/m^2) was 37.5 mg daily and for pemetrexed (500 mg/m^2) was 37.5 mg daily. Reported DLTs included febrile neutropenia, fatigue, hand-foot syndrome, gastrointestinal hemorrhage, cerebral hemorrhage, and ischemic optic neuropathy. Phase I trials evaluating the combination of sunitinib with other targeted agents like temsirolimus (Patel et al., 2009; Fischer et al., 2008), bevacizumab (Feldman *et al.*, 2008; Cooney *et al.,* 2008) and IFN- α (Motzer *et al.,* 2009a) have shown problems with increased toxicity in patients with RCC (Feldman *et al.,* 2008, Fischer *et al*., 2008; Motzer *et al*., 2009a). However, the combination of bevacizumab with sunitinib in patients with miscellaneous solid tumors was well tolerated (Cooney *et al*., 2008).

Phase 2 and 3 Experience

Updated results have recently been published on 750 patients with MRCC treated on a phase 3 study of sunitinib at a daily dose of 50 mg on the 4/2 schedule compared to interferon (IFN)-α 9 MU subcutaneously thrice weekly (Motzer *et al*., 2009b). Median overall survival (OS) was greater in the sunitinib group than in the IFN-α group (26.4 vs. 21.8 months, respectively). Sunitinib treatment was associated with a higher objective response rate (RR) than IFN-α (47% vs. 12%, respectively). Eleven patients in the sunitinib group and four patients in the IFN-α group achieved a complete response per investigator assessment. Median progression-free survival (PFS) was 11 months for sunitinib compared with 5 months for IFN-α. The most commonly reported sunitinib-related grade 3 adverse events included hypertension (12%),

fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%). An exploratory analysis, which censored 25 patients from the IFN-α group who had crossed over to receive sunitinib on study, showed a median OS time of 26.4 months for sunitinib compared with 20 months for the IFN-α group. Results from a phase 1/2 dose-finding trial of sunitinib plus gefitinib, enrolling 42 patients, have been published (Motzer *et al*., 2010). In phase 1, patients received sunitinib 37.5 or 50 mg on the 4/2 schedule plus gefitinib 250 mg, both once daily. The MTD was determined to be 37.5 mg. Two DLTs were observed with the 50 mg dose: grade 2 left ventricular ejection fraction decline and grade 3 fatigue. In phase 2, patients received sunitinib at the MTD plus gefitinib. Thirteen patients treated at the MTD achieved a partial response and 12 had stable disease. Median PFS was 11 months. The most commonly reported grade 3/4 adverse event was diarrhea.

The promising results in phase 1 trials and the involvement of KIT and PDGFR-α, two of the sunitinib target RTKs in GIST led investigators to undertake a phase 1/2 trial in patients with GIST refractory or intolerant to imatinib to determine an appropriate dose and regimen for phase 2 development of sunitinib in this disease. Patients received up to 75 mg sunitinib daily on the 2/2, 4/2, or 2/1 schedule, with 50 mg daily on the 4/2 schedule being selected for continued study. In all, 75 patients were treated on the trial. Among 41 patients treated for at least 6 months, 6 had an objective response (OR; RECIST criteria) and an additional 16 had cessation of disease progression and minor responses for >6 months. Overall, 54% of the 41 patients had evidence of clinical benefit (OR or PFS) (Desai *et al*., 2004). Determination of the GIST genotype in these 41 patients showed that clinical benefit had been achieved in several secondary mutational variants that conferred imatinib resistance (Demetri *et al*., 2004). Fifty-three of the GIST patients treated on this trial subsequently underwent serial ^{18}FDG-PET imaging where qualitative responses were graded as good in 33/53 patients, mixed in 15/53, and poor in 5/53 (Dileo *et al*., 2005). Correlation with clinical response (Fisher's exact p=0.03) showed that 22 of 33 patients graded as good by ^{18}FDG-PET imaging had clinical benefit (OR or SD $\geq$ 6 months) after 6 months of therapy while 4 of 15 patients graded as mixed had benefit as did 2 of 5 patients graded as poor.

Data from a pivotal multinational, randomized (2:1), double-blind, placebo-controlled phase 3 trial in over 300 patients with imatinib-resistant GIST has shown significant clinical effect with sunitinib compared with placebo (Demetri *et al*., 2006). Patients on the active treatment arm received sunitinib at a dose of 50 mg daily on the 4/2 schedule. The median TTP for the treatment arm (n=207) was 27.3 weeks compared to a median of 6.4 weeks for placebo (n=105) (p<0.0001). Therapy was reasonably well tolerated; the most common adverse events were fatigue, diarrhea, skin discoloration and nausea.

In addition to patients with RCC and GIST, sunitinib has been evaluated in breast cancer (Burstein *et al.,* 2008), NSCLC (Socinski *et al.*, 2008), transitional cell carcinoma (TCC) (Gallagher *et al.*, 2008), NET (Kulke *et al.*, 2008), thyroid carcinoma (Cohen *et al.*, 2008), certain subtypes of sarcoma (Keohan *et al.*, 2008; Vigil *et al.*, 2008), gastro-eosophageal cancer (Moehler *et al.*, 2009), high-grade glioma (Chaskis *et al.*, 2008), squamous cell carcinoma of the head and neck (SCCHN) (Choong *et al.*, 2008), hepatocellular carcinoma (HCC) (Zhu *et al.*, 2008), colorectal carcinoma (CRC) (Saltz *et al.* 2007; Starling *et al.*, 2008; Pfeiffer *et al.*, 2009)

and uveal melanoma (Chan *et al.*, 2008). Results from these trials have been summarized in Gan *et al*., 2009.

Clinical Efficacy of Sunitinib in ASPS
Preliminary results from a Phase II trial of sunitinib malate in ASPS have been published, with an update presented at ASCO 2010. Ten patients with advanced ASPS were administered sunitinib at 37.5 mg po qday; 5 patients had PR, and 1 had SD. Responses were >9 months in all cases, with one patient still responsive after 28 months (Stacchiotti *et al*., 2009; Palassini *et al.*, 2010).

A recent case report also describes a patient with aggressive ASPS with lung and bone metastases who had failed multiple chemotherapy regimens prior to treatment with sunitinib. This patient had complete regression of the primary tumor, with stabilization of his bone metastases (Ghose et al. 2010).

Safety Profile
Sunitinib is reasonably well tolerated, with asthenia, hypertension, dermatitis, and mild myelosuppression as the most common AEs (Stadler, 2006). Additionally, the inhibition of TK receptors by agents such as sunitinib can result in cutaneous AEs such as acral erythema, subungal splinter hemorrhages, modification of hair and skin pigmentation, mucositis, and (occasionally) periocular edema (Robert *et al*., 2005; Suwattee, 2008). Hand-foot skin reaction, a group of signs and symptoms that can affect, usually bilaterally, the hands and/or feet of patients, has occurred in patients receiving sunitinib (Porta *et al*., 2007; Suwattee, 2008). A recent analysis of dermatological AEs in patients receiving sunitinib therapy has reported that all-grade hand-foot skin reactions occurred in 19% of patients (5% grades 3-4), skin discoloration in 28% (no grades 3-4), dry skin in 16% (1% grades 3-4), skin rash in 13% (1% grades 3-4), dermatitis in 8% (2% grades 3-4), hair color changes in 10% (no grades 3-4), alopecia in 6% (no grades 3-4), and phototoxicity in <0.1% (no grades 3-4) (Rosenbaum *et al*., 2008).

Cardiotoxicity, including congestive heart failure (3%-8%) and left ventricular dysfunction (12%-14%), has been reported in patients undergoing treatment with sunitinib (Chu *et al*., 2007; Khakoo *et al.*, 2008; Schmidinger *et al.*, 2008; Telli *et al.,* 2008). More subjects treated with sunitinib experienced decline in left ventricular ejection fraction (LVEF) than subjects receiving either placebo or IFN-α (Investigator's Brochure, 2009). In a phase 3 GIST study in subjects with imatinib-resistant or -intolerant GIST, 22 of 209 (11%) subjects on sunitinib and 3 of 102 (3%) subjects on placebo had treatment-emergent LVEF values below the lower limit of normal (LLN). In a phase 3 study treatment-naive RCC patients, 27% and 15% of subjects on sunitinib and IFN-α, respectively, had an LVEF value below the LLN. Among 461 patients enrolled in CDUS-monitored trials with sunitinib alone, 2% of patients experienced left ventricular systolic dysfunction (CDUS data). It is unknown whether patients with concurrent cardiac conditions may be at a higher risk for developing drug-related LVEF. Baseline and periodic evaluations of LVEF should be considered while these patients are on sunitinib treatment. In patients without cardiac risk factors, a baseline evaluation of LVEF should be considered.

Sunitinib has been shown to prolong the QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias, including Torsade de Pointes. This condition has been reported in <0.1% of sunitinib-exposed patients. The DCTD, NCI, issued an IND AE Action Letter to all investigators using sunitinib describing the occurrence of QTc prolongation and Torsade de pointes (ventricular tachycardia) in patients on clinical trials utilizing sunitinib. As a result of this Action Letter, DCTD, NCI-sponsored sunitinib protocols were amended to include the requirement for a baseline EKG prior to study treatment, exclude patients with histories of serious ventricular arrhythmias or prolonged QTc, and exclude patients with certain cardiac conditions.

Among 8054 solid tumor subjects treated with single-agent sunitinib, Grade 3 hypertension was reported in 6.1% of patients and was one of the most commonly reported Grade 3 AEs. Of subjects receiving sunitinib for treatment-naive MRCC, 34% receiving sunitinib experienced hypertension, compared with 4% on IFN-α. Grade 3 hypertension was reported in 13% of treatment-naive metastatic RCC subjects on sunitinib compared to <1% on IFN-α. Severe hypertension occurred in 4% GIST subjects on sunitinib, 1% GIST subjects on placebo, 9% RCC subjects on sunitinib and 1% RCC subjects on IFN-α (Investigator's Brochure, 2009). Among 461 patients enrolled in CDUS-monitored trials with sunitinib alone, 28% experienced hypertension (CDUS data).

In subjects receiving sunitinib for treatment-naive MRCC, 37% had bleeding events compared with 8% receiving IFN-α (Investigator's Brochure, 2009). Bleeding events occurred in 18% of patients receiving sunitinib in the double-blind treatment phase of the GIST phase 3 study, compared with 17% receiving placebo. Among 461 patients enrolled in CDUS-monitored trials with sunitinib alone or in combination with other agents, there were 103 reported bleeding events (CDUS data). Epistaxis was the most common hemorrhagic AE reported. Tumor-related hemorrhage can occur with sunitinib and in the case of pulmonary tumors, may present as severe and life-threatening hemoptysis or pulmonary hemorrhage.

Hypothyroidism has been reported in 71% patients with RCC (Rini et al., 2007) and in 36% of those with GIST (Desai *et al.*, 2006) treated with sunitinib. Among subjects treated with single-agent sunitinib, hyperthyroidism was reported in 0.6% and thyroiditis in 0.1% (Investigator's Brochure, 2009). Baseline measurement of thyroid function is recommended, and patients with thyroid dysfunction should be treated appropriately prior to starting sunitinib therapy. Nonclinical evidence of adrenal toxicity following sunitinib exposure led the company to perform specialized safety assessments in clinical studies, including computed tomography or MRI in 336 subjects to specifically identify any change in adrenal gland structure or the presence of adrenal gland hemorrhage (Investigator's Brochure, 2009). Neither event was observed. Adrenocorticotropic hormone (ACTH) stimulation testing was done in 400 patients across multiple sunitinib trials. One subject developed consistently abnormal test results during treatment that were unexplained and may be related to sunitinib treatment. Eleven additional subjects had abnormalities in the final test, with low peak cortisol levels. None of these patients had clinical evidence of adrenal insufficiency. However, based on the nonclinical findings, patients receiving sunitinib should be clinically followed for signs and symptoms of adrenal insufficiency, especially in (1) patients with comorbidities associated with adrenal dysfunction, (2) patients with preexisting adrenal insufficiency (primary or secondary), and (3) patients with

concomitant stress (e.g., fever, infection, bleeding, serious accident, surgery) that may precipitate overt adrenal insufficiency in the presence of subclinical sunitinib-induced adrenal toxicity. Diarrhea, nausea, abdominal pain, vomiting, constipation and dyspepsia are some of the most frequent AEs reported with sunitinib (Investigator's Brochure, 2009). Serum chemistries including phosphate should be performed at the beginning of each treatment cycle. Supportive care may include anti-emetic premedication, supportive oral care products, and analgesics. Serious complications due to degeneration or shrinkage of tumors, including gastrointestinal perforation and tracheoesophageal fistula, have occurred rarely in patients with abdominal, head and neck, thyroid, and other malignancies treated with sunitinib, believed to be the result of the antitumor effect of sunitinib. Other serious effects include thromboembolic events, rare reversible posterior leukoencephalopathy syndrome (RPLS), proteinuria with rare nephrotic syndrome, and rare microangiopathic hemolytic anemia.

Clinical Pharmacokinetics
Orally-administered sunitinib is well absorbed in humans, with linear pharmacokinetics (PK) at doses of 50-150 mg/day (Sakamoto, 2004). Sunitinib is highly protein-bound and metabolized through *N*-de-ethylation by cytochrome P450 (CYP) 3A4 to SU12662 (Investigator's Brochure, 2009). SU12662 has a similar inhibitory profile to sunitinib *in vitro* and similar protein binding properties. SU12662 is further metabolized by CYP3A4 to a minor inactive metabolite (Investigator's Brochure, 2009).

The PK of sunitinib was studied in a variety of company-sponsored studies in both healthy volunteers (n=135) and in patients with solid tumors (n=266), including GIST and metastatic RCC; the PK was similar in the volunteers and in those with solid tumors. Terminal half-lives ($t_{1/2}$) of sunitinib and SU12662 are 40-60 hours and 80-110 hours, respectively, with a time to maximum concentration (T_{max}) of 6-12 hours for sunitinib and its primary active metabolite, followed by a biexponential decline in concentrations. The PK of sunitinib and SU12662 were measured in a phase 1 dose-escalation study in patients with advanced solid malignancies (Faivre *et al*., 2006). Twenty-eight patients received doses ranging from 15 mg/m^2 to 59 mg/m^2 (ranging from 50 mg every other day to 150 mg/day), on a 4 weeks on, 2 weeks off (4/2) schedule. Concentration-versus-time data were analyzed using a noncompartmental analytic technique. Overall, sunitinib displayed a long half-life and a large volume of distribution with moderate interpatient variability. Trough plasma concentrations of sunitinib and SU12662 increased with increasing doses. However, area under the concentration-time curve (AUC) values increased less than proportionally with dose. Accumulation ratios of sunitinib were >1, with detectable trough drug levels, suggesting drug accumulation over time. At the recommended dose, maximum plasma concentration (C_{max}) occurred approximately 5 hours after administration and $t_{1/2}$ ranged from 41-86 hours. Doses of 50 mg daily led to plasma concentrations ranging from 50-100 ng/mL. Most patients with DLTs had combined (sunitinib plus SU12662) trough plasma concentrations ≥100 ng/mL (Faivre *et al*., 2006).

PK values determined from body surface area (BSA)-based doses were adjusted to reflect fixed doses of 50, 75-100, and 100-150 mg doses to determine if there was a need for BSA-based dosing to be employed. AUC sum values obtained using BSA-normalized and fixed dosing were found to be comparable, suggesting that normalizing the dose based on BSA would not improve

variability. Therefore, fixed dosing on a milligram basis was considered appropriate for phase 2 studies (Faivre *et al*., 2006).

To determine the effect of food on the PK of sunitinib and its active metabolite SU12662, 16 healthy subjects received a single dose of sunitinib 50 mg under fasting conditions and 14 subjects received a single dose of sunitinib 50 mg under fed conditions (Bello *et al*., 2006). Subjects were randomized to one of two treatment sequences each comprising two treatment periods (fasted and fed). In Sequence 1, the fasted treatment period was followed by the fed treatment period, and for Sequence 2, the fasted period followed the fed period. For the fasted period, a single oral (PO) dose of sunitinib 50 mg was administered after a 10-hour fast. For the fed period, a single PO dose of sunitinib 50 mg was administered within 30 minutes of a high-fat, high-calorie meal. A washout period of at least 4 weeks separated sunitinib dosing between the two treatment periods. Two subjects in Sequence 1 discontinued prematurely due to grade 1 and 2 rash, but PK information was collected and included in the analysis. Only a negligible difference in T_{max} of sunitinib was observed between fed and fasted treatment periods; SU12662 T_{max} was prolonged by 2 hours (median difference) in the fed compared with the fasted state. The 90% confidence intervals (CIs) for C_{max} and AUC were within the 80-125% bioequivalence range, indicating the absence of food effect. Sunitinib exposure increased slightly in the fed compared with the fasted state (ratios of fed/fasted geometric least square means: C_{max} 104%, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ both 112%). There was a delay in the formation/absorption of the active metabolite SU12662 in the fed state (mean C_{max} decreased 23%), but exposure remained unaffected (90% CIs for AUC $_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ were within 80-125%). Sunitinib and SU12662 half-lives, and oral clearance of sunitinib, were not affected by food (Bello *et al*., 2006).
A study of sunitinib PK in patients with AML indicated that a plasma concentration of 50-100 ng/mL of combined sunitinib and SU12662 could be achieved on the first cycle of a 50 mg/day 4/2 regimen, similar to that achieved in studies with patients having other tumor types (Fiedler *et al*., 2005).

In a phase 1 trial of sunitinib given on the 4/2 schedule in pediatric patients with relapsed or refractory solid tumors, the median day 21 steady-state trough sunitinib plasma concentration was 24.6 ng/mL (range, 6.0-37.7 ng/mL) at the 15 mg/m^2 dose and 37.4 (range, 24.2-62.9 ng/mL) at the 20 mg/m^2 dose (DuBois *et al*., 2008).

Population PK methods indicated that the covariates of weight, gender, race, ethnicity, ECOG score, and tumor type had no clinically significant effects on drug exposure, and that adjustments of starting doses based on these covariates were not required (Investigator's Brochure, 2009). Concurrent administration of a single dose of sunitinib with ketoconazole (a CYP3A4 inhibitor) in healthy volunteers resulted in 49% and 51% increases in the combined (sunitinib + SU12662) C_{max} and $AUC_{0\text{-}\infty}$ values, respectively, compared with sunitinib alone (Washington *et al*., 2003). Concurrent administration of sunitinib and rifampin (a potent CYP3A4 inducer) in healthy subjects resulted in 23% and 46% reduction in combined C_{max} and $AUC_{0\text{-}\infty}$, respectively, compared with sunitinib alone (Bello *et al*., 2005). Thus, dose adjustments for sunitinib should be considered when co-administered with CYP3A4 inhibitors and inducers.

Proposed Dose and Schedule for Phase II Clinical Trials
Starting doses in multiple-dose studies were 25, 50, 75, and 100 mg administered orally once daily with the majority of patients receiving the 50-mg dose. Patients in sunitinib studies have been treated on four different schedules: schedules 4/1 and 4/2 comprised 4 consecutive weeks of daily dosing followed by a 1- or 2-week rest period, respectively, while schedules 2/1 and 2/2 comprised 2 consecutive weeks of daily dosing followed by a 1- or 2-week rest period, respectively. The majority of subjects were treated on schedules 4/2 or 2/2 in phase 1 studies. Schedule 4/2 has been well tolerated with generally mild to moderate adverse effects at a 50 mg daily dose. Alternate regimens of sunitinib are being explored; 50 mg of sunitinib daily for 2 weeks followed by a 1-week off-treatment period (sunitinib 2/1) (Britten *et al*., 2008), while another schedule is sunitinib 37.5 mg as a CDD (George *et al.,* 2008). Both schedules were well-tolerated, achieved therapeutic plasma concentrations, and showed no significant accumulation of the drug.

2.4 Rationale

There is no effective systemic treatment for patients with metastatic ASPS, but both sunitinib and cediranib are showing preliminary evidence of activity, supporting further clinical investigation (Gardner *et al.*, 2008; Gardner *et al.*, 2009). Given this promising activity, we propose to conduct a randomized trial of cediranib or sunitinib in patients with metastatic ASPS that is not considered to be curable. We plan to enroll 2 sets of patients into separate cohorts for analysis: a) patients with non-newly diagnosed ASPS and b) patients with newly diagnosed ASPS. In each cohort, the ORR and 6-month PFS will be determined separately for patients who receive cediranib and patients who receive sunitinib. At the time of disease progression, patients who received cediranib will be crossed over to receive sunitinib and patients who received sunitinib will be crossed over to receive cediranib, respectively, as long as the treatment arm to which they would cross over remains open. After cross-over, the ORR and rate of disease stabilization will be determined for each agent at 24 weeks; this will provide information about the efficacy of each agent as a second VEGFR inhibitor (although not necessarily as second-line therapy metastatic disease) *and possibly* suggest the appropriate sequencing of these agents in the future.

2.5 Correlative Studies Background

Current knowledge of potential therapeutic targets and their expression pattern in ASPS is limited. Only a few studies of small sample size, using archival pre-treatment tissue, have demonstrated some potentially targetable angiogenic factors (Lazar *et al*., 2007; Stockwin *et al*., 2009) through identification of up-regulated angiogenesis genes such as *angiogenin, HIF1α, TGFβ1, JAG1, midkine, c-MET,* and *VEGF*. Paired pre- and post-treatment tumor biopsies would be of significant benefit in the quest for new target identification. In addition, early data from Phase II studies with single-agent cediranib and sunitinib in patients with ASPS, as well as our own data, merit further understanding of the mechanism of action of these therapeutic agents.

A major limitation to the study of therapeutic targets in ASPS is the rarity of this tumor, making access to human specimens difficult. This study provides the rare opportunity to acquire tissue. Paired pre- and post-treatment tumor biopsies would be of significant benefit in providing insight into the mechanisms of action of cediranib and sunitinib by allowing detection of gene

alterations after treatment and by comparing findings with clinical outcome. Only patients enrolled at the Clinical Center, NCI will be asked to give biopsies; tumor biopsies are optional. *With Amendment H (version dated 11/20/2013), biopsies will no longer be performed on this study. Language referencing biopsy collection has been left in the protocol for historical reference purposes.*

3 PATIENT SELECTION

3.1 Eligibility Criteria

Status Update: Patients enrolled after Amendment G (version dated 08/16/2013), will be evaluated and compared to the first 13 patients by the study statistician and the Principal Investigator.

- Patients must have histologically confirmed metastatic alveolar soft part sarcoma that is not curable by surgery. Diagnosis of malignancy must be confirmed by the department of pathology at the institution where the patient is enrolled prior to patient enrollment.
- Patients must show evidence of objective disease progression per RECIST 1 on scans within the 6 month period immediately preceding enrollment. Both scans used to determine disease progression should have been obtained within this 6-month period.
- Patients with newly diagnosed, unresectable, metastatic, and measurable ASPS who show clinical evidence of disease progression (including history and increasing physical symptoms) will also be eligible. On-study documentation will include a physician's rationale that supports evidence of clinical disease progression (i.e., increasing tumor pain).
- Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See Section 11 for the evaluation of measurable disease.
- Any prior therapy must have been completed ≥ 4 weeks prior to enrollment on protocol and the participant must have recovered to eligibility levels from prior toxicity. Patients should be at least 6 weeks out from nitrosoureas and mitomycin C. Prior radiation should have been completed ≥ 4 weeks prior to study enrollment and all associated toxicities resolved to eligibility levels. Patients who have had prior monoclonal antibody therapy must have completed that therapy at least 3 half-lives of the antibody or 6 weeks ago. Patients who have received more than a cumulative dose of 350 mg/m^2 of doxorubicin may be enrolled at the discretion of the Coordinating Center PI after consultation with a cardiologist and if screening echocardiogram is normal.
- Patients must be ≥ 2 weeks since any investigational agent administered as part of a Phase 0 study (also referred to as an "early Phase I study" or "pre-Phase I study" where a sub-therapeutic dose of drug is administered) at the Coordinating Center PI's discretion, and should have recovered to eligibility levels from any toxicities.
- Patients with no prior therapy are eligible, provided they have metastatic disease that is not curable by surgery.

- Age ≥ 16 years. Patients age 16-17 years are eligible only if they have a BSA ≥1.7 m^2 or weigh ≥60 kg.
- ECOG performance status ≤ 2 (Appendix A).
- Life expectancy of greater than 3 months.
- Patients must have normal organ and marrow function as defined below:

o leukocytes	≥3,000/mcL
o absolute neutrophil count	≥1,500/mcL
o platelets	≥100,000/mcL
o hemoglobin	≥9 g/dL
o total serum bilirubin	within normal institutional limits
o AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
creatinine	within normal institutional limits
	OR
o creatinine clearance	≥60 mL/min for patients with creatinine levels above institutional normal

- QTc <480 msec (with Bazett's correction) in screening electrocardiogram.
- The following groups of patients are eligible after consultation with a cardiologist and at the Coordinating Center PI's discretion, provided they have New York Heart Association Class II (NYHA; see Appendix B) cardiac function on baseline ECHO:
  - those with a history of Class II heart failure who are asymptomatic on treatment
  - those with prior anthracycline exposure greater than a cumulative dose of 350 mg/m^2
  - those who have received central thoracic radiation that included the heart in the radiotherapy port.
- Patients must have blood pressure (BP) no greater than 140 mmHg (systolic) and 90 mmHg (diastolic) for eligibility. Initiation or adjustment of BP medication is permitted prior to study entry provided that the BP reading prior to enrollment is no greater than 140/90 mmHg.
- Left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal.
- Because sunitinib is metabolized primarily by the CYP3A4 liver enzyme, strong CYP3A4 inhibitors are not permitted within 7 days before and during the study, and strong CYP3A4 inducers are not permitted within 12 days before and during the study. A list of drugs that may interact with the cytochrome P450 system is included in Appendix C. Every effort should be made to switch patients taking such agents or substances to other medications 1 week prior to starting therapy, particularly patients with brain metastases who are taking enzyme-inducing anticonvulsant agents (Appendix D). Patients who require potent CYP3A4 inducers or inhibitors and cannot switch medications must have their case reviewed by the Coordinating Center PI and may be enrolled only after discussion with and agreement from the Coordinating Center PI. Current clinical studies with cediranib have

not found clinically significant effects on cediranib PK with co-administration of CYP3A4 inducers or inhibitors. Eligibility of patients receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics (PK) of cediranib will be determined following review of their case by the Coordinating Center PI.

- Both study agents have been shown to terminate fetal development in the rat, as expected for a process dependent on VEGF signaling. For this reason, women of childbearing potential must have a negative pregnancy test prior to study entry. Women of child-bearing potential and men must agree to use two reliable forms of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 2 months following study drug discontinuation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
- Patients who are nursing infants: because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with study agents, breastfeeding should be discontinued if the mother is treated with the study agents.
- Ability to understand and the willingness to sign a written informed consent document.
- Patients must be able to swallow whole tablets and capsules.

3.2 Exclusion Criteria

- Patients must not have received prior treatment with any VEGF receptor tyrosine kinase inhibitor (e.g., cediranib, sunitinib, pazopanib, sorafenib); however, prior treatment with bevacizumab is allowed.
- Patients may not be receiving any other investigational agents.
- Major surgery within 4 weeks prior to entry into the study, or a surgical incision that is not fully healed.
- History of familial long QT syndrome, or use of medications that may cause QTc interval prolongation (Appendix E).
- Patients with a pre-existing thyroid abnormality who are unable to maintain thyroid function in the normal range with medication are ineligible.
- Warfarin and its derivatives are not allowed. Patient can be receiving low molecular weight heparin if clinically indicated.
- Uncontrolled intercurrent illness including, but not limited to hypertension, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Patients with any condition (e.g., gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, or active peptic ulcer disease) that impairs their ability to swallow, retain, and/or absorb the drug are excluded.
- Patients with any of the following conditions are excluded: serious or non-healing wound, ulcer; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment; coronary/peripheral artery bypass graft or stenting within the

past 12 months; or cerebrovascular accident (CVA) or transient ischemic attack within the past 12 months.

- Greater than 2+ proteinuria on two consecutive dipsticks taken no less than 1 week apart or 24-hour urine protein of > 1 g. Patients with < 2+ proteinuria are eligible following initial determination by urinalysis within 1 week prior to enrollment and do not need the urinalysis repeated.
- HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for PK interactions with cediranib or sunitinib. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Research Eligibility Evaluation

3.3.1 Clinical Evaluations

- A complete history and physical examination will be completed within 8 days prior to subject enrollment. This will include determination of performance status.
- EKG will be done for determination of QTc within 8 days prior to subject enrollment.
- Echocardiogram scan for determination of LVEF within 28 days prior to subject enrollment.
- Diagnostic imaging studies must be performed within 28 days prior to enrolling on study. This will include appropriate imaging studies for tumor measurement.

3.3.2 Laboratory Evaluations

Laboratory tests to establish eligibility should be performed within 8 days prior to subject enrollment unless stated otherwise.

- Hematological profile: CBC with differential and platelet count
- Biochemical profile: albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, glucose, magnesium, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium, TSH
- Troponin T or I
- Urinalysis
- Urine pregnancy test in women of childbearing potential

3.3.3 Pathology Review

A block or 6 unstained slides of primary tissue will be required from each study subject to confirm diagnosis. Tissue blocks from a known recurrence will be accepted if the original tumor samples are unavailable. Diagnosis of malignancy must be confirmed by the department of pathology at the institution where the patient is enrolled.

3.4 Inclusion of Women and Minorities

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. For safety reasons, pregnant women and children age <16 years are excluded from this study. Efforts will be made to extend accrual to each representative population. If differences in outcome that correlate to ethnic identity are

noted, a follow-up study may be written to investigate those differences more fully. This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. Accrual targets are listed below.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	6	+	6	=	12
Not Hispanic or Latino	21	+	14	=	35
Ethnic Category: Total of all subjects	27 (A1)	+	20 (B1)	=	47 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	2	+	2	=	4
Black or African American	3	+	3	=	6
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	22	+	15	=	37
Racial Category: Total of all subjects	27 (A2)	+	20 (B2)	=	47 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

Accrual Rate: 1 pts/month **Total Expected Accrual:** 44 Min 47 Max

4 REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	

Documentation Required	IVR	NPIVR	AP	A
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

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

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

4.2 Patient Registration

Eligible participants will be entered on study by a member of the Coordinating Center study team.

4.2.1 Coordinating Site Registration Process

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates, found here: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825

Cohorts:
Cohort 1, Non-newly Diagnosed
Cohort 2, Newly Diagnosed

Arms:
Arm 1, Part I
Arm 2, Part II

Arm Assignment:
Subjects in cohorts 1 and 2 will be assigned to arm 1, and may cross over to arm 2 when they come off arm 1.

4.2.2 Participating Site Registration

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates, found here:
https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825

To register a patient after they have signed the consent, complete Appendix F (Eligibility/Pre-Registration Worksheet) and fax (or email) it, along with all supporting records to the Coordinating Center's Research Nurse, Ashley Bruns, Phone: (240) 858-3162, ashley.bruns@nih.gov. The Coordinating Center will notify you either by e-mail or fax that the protocol registration form has been received. The Coordinating Center will register the patient and provide the participating site with the patient's unique patient ID number. This unique ID number is to be used on all research samples and data entry for this patient. Questions about eligibility should be directed to the Coordinating Center's Research Nurse, Ashley Bruns, Phone: (240) 858-3162, ashley.bruns@nih.gov.

4.2.3 Randomization Procedure

The subject will be randomized by the Coordinating Center using a predetermined, balanced list. During randomization, the unique subject identifier (subject number / subject ID) will be submitted to the randomization node; the randomization node will select the next available treatment assignment, record the subject number in the list, and return the treatment arm associated with the selected randomization record. Once a randomization number has been assigned, it will not be reused.

4.2.4 Off Protocol Therapy and Off-Study Procedure

Status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates, found here:
https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825

Participating sites: When a patient is taken off protocol therapy and when a patient is taken off-study, the Participant Status Updates Form included in Appendix F must be completed and faxed or emailed to the Coordinating Center's Research Nurse, Ashley Bruns, Phone: (240) 858-3162, ashley.bruns@nih.gov.

5 TREATMENT PLAN

Patients enrolled after Amendment G (version dated 08/16/2013), will be evaluated and compared to the first 13 patients by the study statistician and the Principal Investigator. PFS at 24 weeks will be calculated for all the study participants and for the initial 13 patients and the rest of the patients separately to assess for any differences. Patients with newly diagnosed ASPS and clinical evidence of disease progression will also be assessed separately.

This is a randomized, open-label Phase II trial of cediranib and sunitinib in patients with ASPS. Patients will be randomized at study entry (Part I) to receive cediranib (30 mg) or sunitinib (37.5 mg) orally, once a day, in 28-day cycles. *As of Amendment Y (dated May 6, 2019), we have closed the cediranib arm of the newly diagnosed ASPS cohort due to inadequate activity; all newly diagnosed ASPS patients will be assigned to the sunitinib malate treatment arm.*

At the time of disease progression (documented by RECIST 1), patients will cross over to the other treatment arm (Part II) after a 2-week wash-out period. However, if the other treatment arm has been closed due to inadequate activity (as defined in Section 13) or unacceptable toxicity, patients will not be eligible to cross over to that arm and will receive no further treatment on study. During Part II, patients will receive the other agent, cediranib (30 mg) or sunitinib (37.5 mg), orally, once a day, in 28-day cycles. Both arms will be analyzed independently for the primary and secondary endpoints. *As of Amendment Y (date May 6, 2019), we have closed the cediranib arm of the newly diagnosed ASPS cohort due to inadequate activity; patients in this cohort are not eligible to cross over to the cediranib arm.*

If the patient has disease progression that would require palliative radiation therapy (i.e., bone or brain) then crossover to the other arm can be delayed until the palliative radiation therapy is completed. There will be a minimum wash out period of 2 weeks after completion of radiation therapy. Crossover to Part II of the protocol can be delayed up to 6 weeks to allow the patient to recover from the side effects of treatment. Patients will be required to meet all eligibility criteria prior to crossover. No data or adverse events that result from radiation therapy will be captured.

Appropriate anatomic imaging studies will be performed at baseline (within 28 days prior to start of protocol therapy), and imaging studies from the eligibility screening may be used if they are within this time period. Repeat imaging scans will be performed every 2 cycles. Responses will be confirmed according to the RECIST 1.0 (Section 11), with restaging scans at least 4 weeks apart. Independent radiology review will be arranged of patient scans (including eligibility scans demonstrating disease progression prior to enrolling). Copies of anatomic imaging scans will be maintained by the research teams to facilitate radiology review.

Patients will be provided with a Study Diary (Appendix G), instructed in its use, and asked to bring it with them, along with any unused drug, to each appointment. A new copy of the Study Diary will be given to patients who cross over to the other treatment arm (Part II) and to patients whose dose is reduced due to adverse events.

Blood pressure will be monitored every 2 weeks by any health care provider during the first cycle of Part I and Part II, then at least at the start of every cycle for the duration of treatment (unless patients have experienced elevated blood pressure requiring drug therapy, at which point the frequency of BP monitoring by a health care provider will be determined by the local PI). Patients who have been on study for more than two years will have blood pressure monitored at the start of every third cycle. Additionally, all patients will be required to monitor their BP at home at least once a day while on study and record the readings in the Study Diary (Appendix G). (See Section 6 for hypertension management and dose reduction.)

Patient evaluations will be performed throughout the study as described below. Baseline history, physical examination, laboratory evaluations, and EKG must be conducted within 8 days prior to start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations (see Section 3.3.1 and Section 3.3.2), the results from these screening evaluations may be used as baseline measurements. If >8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, and EKG must be repeated prior to starting protocol therapy.

Labs (CBC with differential, serum chemistries) will be performed every 2 weeks for the first 2 cycles of Part I and Part II, and then at the start of every cycle for the duration of treatment. Patients who have been on study for more than two years will have labs performed at the start of every third cycle.

EKGs and ECHOs will be performed at baseline (within 8 and 28 days prior to start of protocol therapy, respectively), and prior to patients starting on Part II, and as clinically indicated; EKGs will be performed at the start of every cycle (every three cycles for patients on study longer than 2 years). Routine monitoring for cardiac function (ECHO) will be performed every other cycle of treatment in the following groups of patients: (1) those entering the trial with NYHA Class II cardiac dysfunction (see Appendix B), (2) those with a history of Class II heart failure who are asymptomatic on treatment, and (3) in those previously exposed to anthracyclines or thoracic irradiation if the heart was included in the radiotherapy port.

Patients with bulky solid tumors should be monitored closely for pneumothorax, intestinal fistulae, or intestinal perforation in the event of rapid tumor destruction.

At the end of the study, blocks or stained slides of primary soft tissue will undergo central pathology review by a pathologist with expertise in evaluation of soft tissue sarcomas. Six sections of archival tissue should be sent to the Coordinating Center's Research Nurse using the shipping manifest in Appendix N.

Sparse PK evaluation for cediranib has been added to the study. (See Appendix O: PK Evaluation for Cediranib)

5.1 Drug Administration

At a given time, a patient will be receiving cediranib **OR** sunitinib orally, once a day, in 28-day cycles. (Start of next cycle may be changed by 1 day or delayed for up to 1 week to accommodate scheduling conflicts.) Treatment will be administered on an outpatient basis. After cycle 2, a cycle will be considered completed if 90% of the prescribed doses are administered. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No other investigational or commercial agents may be administered with the intent to treat the patient's malignancy. Tablets and capsules must be swallowed whole. Should the patient vomit within 15 minutes of taking the study drug, the dose should be repeated. If patient vomits more than 15 minutes after taking the study drug, then no additional medication should be taken. A missed dose can be taken

within 3 hours of the usual dosing time; if more than 3 hours have passed, the missed dose should not be made up. If a patient misses a dose, he or she should be instructed to resume dosing with the next scheduled dose.

5.1.1 Cediranib Administration

- Patients will take 30 mg cediranib orally, once daily on an empty stomach (at least 1 hour before or 2 hours after meals). The drug should be taken at approximately the same time each day.

5.1.2 Sunitinib Administration

- Patients will take 37.5 mg sunitinib orally, once daily in the morning, with or without food, as desired. Patients should be alerted to the possibility that sunitinib capsules can cause a yellow discoloration of the skin on direct contact. If this happens, the patient should wash immediately with soap and water.

- Although adrenal gland insufficiency is rarely seen with sunitinib treatment, patients should be clinically followed for the signs and symptoms of this complication, especially (1) patients with comorbidities associated with adrenal dysfunction, (2) patients with pre-existing adrenal insufficiency (primary or secondary), and (3) patients with concomitant stress (e.g., fever, infection, bleeding, serious accident, surgery) that may precipitate overt adrenal insufficiency in the presence of subclinical sunitinib-induced adrenal toxicity. If clinically indicated, objective testing for adrenal gland function should be conducted.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 CYP3A4 Inhibitors and Inducers

The case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies, including herbal supplements, specifically, St. John's wort. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected P450 isoenzymes. (A comprehensive list of CYP3A4-interactive agents is provided in Appendix C.)

Efforts should be made to switch patients who are taking enzyme-inducing anticonvulsant agents (Appendix D) to other medications at least 1 week before the study, and these medications should be avoided as much as possible during treatment.

Eligibility of patients receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics (PK) of cediranib will be determined following review of their case by the Coordinating Center PI. Current clinical studies with cediranib have not found clinically significant effects on cediranib PK with co-administration of CYP3A4 inducers or inhibitors.

Co-administration of potent inhibitors or inducers of CYP3A4 can result in significant changes in exposure to sunitinib (e.g., a mean 1.8-fold increased exposure with ketoconazole and a mean 4-fold decrease with rifampin). For this reason, the following agents should be avoided up to

12 days before and during the study for patients enrolled on either arm of the study. Patients who require such medication and cannot be switched must have their case reviewed by the Coordinating Center PI, and may be administered only after discussion with and agreement from the Coordinating Center PI.

Inhibitors – prohibited 1 week before and during the study

azole antifungals (ketoconazole, itraconazole)	verapamil
clarithromycin	HIV protease inhibitors (indinavir, saquinavir, ritonavir, atazanavir, nelfinavir)
erythromycin	delavirdine
diltiazem	

Inducers – prohibited 12 days before and during the study

rifampin	phenytoin
rifabutin	St. John's wort
carbamazepine	
phenobarbital	

Aprepitant, fluconazole, and voriconazole are clinically relevant moderate CYP3A4 inhibitors that should be avoided, if possible, or used with great caution.

Systemic steroid use is not recommended during sunitinib treatment unless absolutely necessary (e.g., for treatment of adverse events or protocol-required premedication) because many steroids (e.g., prednisone, prednisolone, dexamethasone, etc.) effectively lower sunitinib exposure through CYP3A4 interactions. Topical and intranasal steroids are allowed. Corticosteroid therapy is permissible only for treatment of increased intracranial pressure or for hormonal replacement and should not be used as a prophylactic antiemetic.

In addition, patients and their caregivers should be provided the patient information sheet (Appendix L) describing potential interactions of sunitinib with other drugs, remedies, and medications.

5.2.2 Anti-epileptic Drugs

Anti-epileptic drugs may be used, if indicated. Efforts should be made to switch patients who are taking enzyme-inducing anticonvulsant agents (Appendix D) to other medications at least 1 week prior to administration of cediranib and during administration, and these medications should be avoided as much as possible during treatment. Patients requiring a change in anticonvulsants once on therapy should be switched to an anticonvulsant with a similar effect on hepatic enzymes.

5.2.3 Febrile Neutropenia

Patients with neutropenic fever or infection should be evaluated promptly and treated with IV antibiotic therapy or therapeutic colony-stimulating factors as appropriate following the ASCO guidelines (Smith *et al.*, 2006). Packed red blood cell and platelet transfusion should be

administered as clinically indicated. Erythropoietic agents may be used at the discretion of the treating physician. Measures include laboratory testing, blood and urine cultures, and institution of broad-spectrum antibiotics.

5.2.4 Growth Factors

Routine use of growth factors (i.e., Filgrastim, Sargramostim, Erythropoietin) is not permitted. However, therapeutic use of filgrastim or sargramostim may be considered at the investigator's discretion and administered according to accepted American Society of Clinical Oncology (ASCO) guidelines.

5.2.5 Anti-emetics

Patients with treatment-related nausea should be treated initially with a phenothiazine (prochlorperazine – 10 mg every 6 hours orally as needed or promethazine – 12.5-25 mg IV every 6 hours as needed). If this is inadequate, a benzodiazepine should be added until acute nausea is controlled or toxicity is limiting. Should this prove inadequate acutely, a steroid may be added (e.g., dexamethasone 4 mg every 6 hours as needed).

5.2.6 Anti-diarrheals

If diarrhea develops and does not have an identifiable cause other than study drug administration, anti-diarrheals such as Lomotil (diphenoxylate HCl 2.5 mg plus atropine sulfate 0.025 mg/tablet) dosed according to package insert or loperamide 4 mg po after the first unformed stool with 2 mg po every 2 hours as long as unformed stools continue (4 mg every 4 hours while asleep). No more than 16 mg of loperamide should be taken in during a 24-hour period. This regimen can be repeated for each diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 24 hours ≤ to Grade 2 with the above regimen (16 mg, or less if there is resolution of the symptoms, of loperamide in a 24-hour period).

5.2.7 Agents With Proarrhythmic Potential

Use of agents with pro-arrhythmic potential (Appendix E) is not permitted during the study. A comprehensive list of agents with proarrhythmic potential can be found at http://www.azcert.org/index.cfm.

5.2.8 Hand-Foot Syndrome

Hand-foot syndrome may be treated with topical emollients (such as Aquaphor), topical/systemic steroids, and/or antihistamine agents. Vitamin B6 (pyridoxine; 50-150 mg orally each day) may also be used. Avoid exposure to heat, hot water, pressure, or friction. Use of soft, well-fitting shoes may help, as may use of acetaminophen if needed for analgesia.

5.2.9 Abnormal Thyroid Function

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 the 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 will 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 will be monitored frequently and the dose of levothyroxine titrated as required.

5.2.10 Anticoagulants

The use of coumarin-derivative anticoagulants such as warfarin (Coumadin®) is not recommended, although doses of up to 2 mg daily are permitted for prophylaxis of thrombosis.

5.2.11 Supportive Care Guidelines

- Frequent blood pressure (BP) monitoring is important in patients receiving cediranib. Experience to date suggests that increases in blood pressure may occur following dosing with cediranib for a number of weeks and that these increases may occur over a relatively short time frame. It is imperative that the investigator institute appropriate measures to control BP. This may necessitate changes to existing antihypertensive medication, addition of new medication(s), and/or interruption/withdrawal of cediranib. Section 6 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension. Recommendations for hypertension monitoring and management are presented in Appendix I.
- Renal function (creatinine and urinary protein) should be frequently monitored as suggested by the pathologic changes noted in animal studies and evidence from studies of other anti-angiogenic agents. Specific guidelines for management of proteinuria are presented in Section 6.
- Patient levels of troponin T or troponin I should be monitored because of the potential for myocardial injury with cediranib as clinically indicated.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), subjects may continue on the study as long as they are tolerating the drugs and responding to treatment, or until one of the following criteria are met:

- Disease progression during Part II of the study,
- Intercurrent illness that prevents further administration,
- More than 2 dose reductions required for toxicity in Part II of the study (patients taken off treatment during Part I have the option to cross over to Part II of the study),
- Patient completed Part I of the study (due to toxicity or disease progression) and the other treatment arm has been closed due to inadequate activity (as defined in Section 13) or unacceptable toxicity,
- Pregnancy,
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the opinion of the principal investigator.

5.4 Duration of Follow-up

Patients will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Unacceptable toxicities (i.e., AEs related to the intervention) that have not resolved by Day 30 post-treatment will be followed via biweekly phone calls until stabilization or resolution.

5.5 Criteria for Removal From Study

Patients will be removed from study for one of the following reasons: completed 30-day follow-up period, toxicities are unresolved but stabilized, patient enrolls on another protocol, or patient receives standard of care. The reason for study removal and the date the patient was removed must be documented in the Case Report Form and communicated to Central Registration per Section 4.4.

6 DOSING DELAYS/MODIFICATIONS

6.1 Dose Modifications

Doses will be held or modified only for adverse events that are felt to be at least possibly related to study drug. Exacerbation of tumor pain can occur with administration of study drugs; dose reduction of study drugs will not be required for grade 3 or 4 tumor pain.

Dose will be held and/or modified (as defined below) for grade 3 or greater non-hematologic toxicity (except electrolyte abnormalities unless these are not correctable within 48 hours and tumor pain unless refractory to supportive measures) and/or grade 4 hematologic toxicity (except lymphopenia, anemia). Treatment once held, will not be re-initiated until toxicities resolve to grade 2 or less. Up to 14 days will be allowed for resolution of toxicity, otherwise patients will be taken off treatment.

Please note: Sunitinib should NOT be re-administered if subjects develop ≥ grade 3 hepatic failure per CTCAE v5.0 definition. (Please see the company's prescribing information regarding hepatotoxicity at www. sutent.com.)

If administration of study drug is interrupted for any reason, counting of the cycle days continues (i.e., if a patient stops drug on Day 15 and resumes 2 days later, they will be considered on Day 17).

During Part I and Part II, patients will be started on the initial dose of 30 mg cediranib **OR** 37.5 mg sunitinib orally, once per day for 28 days, in 28-day cycles. Up to 2 dose reductions will be permitted before a patient is taken off treatment. Patients taken off treatment for toxicity during Part I have the option to cross over to Part II of the study (after a 2-week wash-out

period), as long as the other arm has not been closed due to inadequate activity (as defined in Section 13) or unacceptable toxicity.

Dose Modification Table:

Dose Level	Cediranib Dose (mg/day)	Sunitinib Dose (mg/day)
1	30	37.5
-1	20	25
-2	15	25 mg/day, 3 weeks on, one week off

6.2 Cediranib

6.2.1 General Management of Adverse Events

Note: General Management guidelines refer to all AEs except those mentioned otherwise. See Appendix I for hypertension management. For management of reversible posterior leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome, and cardiac toxicity, please refer to Section 6.4. Toxicities will be managed according to standard medical practice.

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
1. Grade 3 or higher (non-hematologic or grade 4 (hematologic) AE related to cediranib and lasting >5 days that does not resolve to grade 2 or below despite maximum supportive care for ≤ 48 hours. 2. Lower grade but related AEs (e.g., proteinuria)	Reduce one dose level*
AE does not resolve to grade 2 or below after treating patient at the lowest (i.e., 15 mg qd) reduced dose level.	In general, remove patient from study
* Alternatively and if medically appropriate, investigators may choose to hold dose for up to 14 days or withdraw patient from study.	

6.2.2 Management of Hypertension

Increases in BP and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following cediranib treatment has been seen in animal studies as well as clinical trials. Specific guidance for management of this AE is provided in Appendix I; additional suggestions for BP collection/recording can be found in Appendix H.

Notes:

- While patients are receiving treatment with cediranib, the early initiation of antihypertensive treatment for grade 2 hypertension to minimize more severe or

persistent hypertension is not considered a grade 3 AE.

- Decisions to hold or decrease the cediranib dose during treatment must be based on BP readings taken in the clinic by a medical professional.

6.2.3 Management of Proteinuria

CTCAE v5.0 will be used for grading of proteinuria. Although patients with ≥ 2+ proteinuria at entry are ineligible, increases in proteinuria may occur during treatment and should be managed as follows:

- During treatment if a patient has two consecutive two plus (++) urine protein dipstick measurements, or one three plus (+++) or greater measurement, a 24-hour urine specimen or urine protein/creatinine ratio sample should be collected. A urine protein/creatinine ratio of 0.15 (urine protein and urine creatinine expressed in mg/dL) approximates a 24-hour urine protein of 150 mg/24 hours or 0.15g/24 hours, which is the upper limit of normal (Rodby *et al.*, 1995; Schwab *et al.*, 1987; Wingo and Clapp, 2000).
- If 24-hour proteinuria or urine protein creatinine ratio is classified as CTCAE grade 3, please follow the general guidance in Section 6.2.1 which has general guidance on CTCAE Grade 3 toxicities. If nephrotic syndrome occurs, cediranib should be permanently discontinued.

6.3 Sunitinib

6.3.1 Management of Treatment-Emergent Hypertension

Increases in blood pressure (BP) and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following sunitinib treatment has rarely been seen in animal studies or clinical trials. Specific guidelines for management of this adverse event and a table of various antihypertensive medications are provided in Appendix I. In addition, guidance on the collection and recording of BP information is provided in Appendix H.

6.3.2 Other Hematologic and Non-Hematologic Adverse Events

Event	AE Grade or Observation	Dose modification
Neutropenia	Grades 1 and 2	Maintain dose
	Grade 3*	Hold sunitinib until ≤ grade 2, then resume at same dose level
	Grade 4	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment
Thrombocytopenia	Grades 1 and 2	Maintain dose
	Grade 3* and severe grade 2, at investigator discretion	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment
	Grade 4	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment
Fever or flu-like symptoms	Grades 1-4	Maintain dose
Fatigue (lethargy, malaise, asthenia)	Grades 1 and 2	Maintain dose
	Grade 3* and severe grade 2, at investigator discretion	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment
QTc prolongation Do not use CTCAE v5 grades	>450 but < 550 msec	Review patient's concomitant medications for QT interval-prolonging agents. Correct any electrolyte abnormalities. Continue sunitinib at current dose level.
	≥ 550 msec	Stop sunitinib and any other QT-interval prolonging agents immediately. Correct any electrolyte abnormalities , then: If there is a plausible explanation for AE other than sunitinib treatment, resume sunitinib at current dose level. If sunitinib **may have contributed** to the AE: Reduce 2 dose levels and restart sunitinib. If QTc remains <500 msec after 14 days at reduced dose, then increase one dose level and continue sunitinib. If QTc remains <500 msec after another 14 days, then the original dose of sunitinib may be resumed.
Hand-foot syndrome	Grades 1 and 2	Maintain dose
	Grade 3*	Hold sunitinib until ≤ grade 1, then resume treatment at same dose or reduce 1 dose level
AST and/or ALT elevation (SGOT, SGPT)	Grades 1 and 2	Maintain dose
	Grades 3 and 4	Sunitinib should be dose delayed if elevation of ALT is >5 × ULN, AST is >5 × ULN, and/or bilirubin is >3 × ULN. Sunitinib may be re-administered when levels of ALT and AST are ≤5 × ULN and bilirubin is ≤3 × ULN. Sunitinib should NOT be re-administered if subjects develop ≥ grade 3 hepatic failure (CTCAEv5 definition). Patients must have LFTs checked at baseline and during each treatment cycle. LFTs should be obtained at any time when they are clinically indicated.

*Recurrent grade 3 events require dose reduction.

6.3.3 Management of Other Clinically Significant AEs (not specifically addressed above)

Sunitinib should NOT be re-administered if subjects develop ≥ grade 3 hepatic failure per CTCAE v5.0 definition. Please see the company's prescribing information regarding hepatotoxicity at www.sutent.com.

Note: General Management guidelines refer to all AEs except those mentioned otherwise. For management of reversible posterior leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome, and cardiac toxicity, please refer to Section 6.4. Toxicities will be managed according to standard medical practice.

General Management Guidelines

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
1. Grade 3 or higher (non-hematologic or grade 4 (hematologic) AE related to sunitinib and lasting >5 days that does not resolve to grade 2 or below despite maximum supportive care for ≤ 48 hours. 2. Lower grade but related AEs (e.g., creatinine)	Reduce one dose level
AE does not resolve to grade 2 or below after treating patient at the lowest (i.e., 25 mg/day, 3 weeks on, one week off) reduced dose level.	In general, remove patient from study

6.4 Dose Reduction

6.4.1 Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome

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

RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with cediranib therapy (<3%) as well as other VEGFR agents. Clinical presentations are variable and may include altered mental status, seizure, and cortical visual deficit. Hypertension is a common risk factor and was present in most (though not all) patients on cediranib who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the

differential diagnosis in patients presenting with unexplained mental status changes, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of blood pressure and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

6.4.2 Cardiac Toxicity

For patients who develop compromised LVEF:

1. Discontinue cediranib or sunitinib in patients who develop symptomatic heart failure;
2. Modify the cediranib or sunitinib dose using the table presented in Appendix J.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Comprehensive Adverse Events and Potential Risks Lists

7.1.1 CAEPR for Cediranib (AZD2171, NSC 732208)

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

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

Version 2.15, November 7, 2018[1]

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Heart failure	

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Left ventricular systolic dysfunction	
ENDOCRINE DISORDERS			
	Hyperthyroidism		
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis		***Anal mucositis (Gr 2)***
	Constipation		***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dysphagia		***Dysphagia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal perforation[3]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
		Pancreatitis	
	Rectal mucositis		***Rectal mucositis (Gr 2)***
	Small intestinal mucositis		***Small intestinal mucositis (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lymphocyte count decreased		
	Neutrophil count decreased		

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Platelet count decreased		
	Thyroid stimulating hormone increased		***Thyroid stimulating hormone increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Generalized muscle weakness		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
	Lethargy		
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 4)***
	Vascular disorders - Other (hemorrhage)[5]		

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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (polycythemia); Bone marrow hypocellular; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (premature ventricular complexes); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Mobitz (type) II atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ears feel full/plugged); Ear and labyrinth disorders - Other (viral labyrinthitis); Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (blindness); Eye disorders - Other (visual disturbance); Papilledema; Photophobia; Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Bloating; Colitis; Colonic obstruction; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Flatulence; Gastric necrosis; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (hydrops); Gastrointestinal disorders - Other (tongue sensitivity); Ileus; Oral pain; Periodontal disease; Peritoneal necrosis; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Fever; Gait disturbance; Hypothermia; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder obstruction; Hepatic pain; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice cholestatic)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Immune system disorders - Other

(systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture; Injury, poisoning and procedural complications - Other (tracheostomy malfunction); Intestinal stoma leak; Venous injury; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Hemoglobin increased; INR increased; Investigations - Other (elevated ammonia level); Investigations - Other (increased blood erythropoietin); Lipase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Avascular necrosis; Back pain; Bone pain; Chest wall pain; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Myalgia; Myositis; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Central nervous system necrosis; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Encephalopathy; Hydrocephalus; Ischemia cerebrovascular; Memory impairment; Muscle weakness left-sided; Nervous system disorders - Other (coma); Nervous system disorders - Other (right hemiparesis); Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Spinal cord compression; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Confusion; Delirium; Depression; Hallucinations; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Cystitis noninfective; Hematuria; Urinary retention; Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Menorrhagia; Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fistula; Pulmonary hypertension; Sinus pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pruritus; Purpura; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (petechiae); Skin and subcutaneous tissue disorders - Other (plantar warts); Skin ulceration; Urticaria
VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hypotension; Vasculitis

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

7.1.2 CAEPR for Sunitinib Malate (NSC 736511)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are

protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 7115 patients.* Below is the CAEPR for Sunitinib malate (SU011248 L-malate).

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 2.14, February 15, 2019[1]

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
ENDOCRINE DISORDERS			
		Endocrine disorders - Other (thyroiditis)	
		Hyperthyroidism	
	Hypothyroidism		***Hypothyroidism (Gr 2)***
EYE DISORDERS			
		Eye disorders - Other (macular edema)	***Eye disorders - Other (macular edema) (Gr 2)***
	Papilledema		***Papilledema (Gr 2)***
		Vision decreased	***Vision decreased (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension (Gr 2)***
Abdominal pain			***Abdominal pain (Gr 3)***
Anal mucositis			***Anal mucositis (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
Dyspepsia			***Dyspepsia (Gr 2)***
		Esophagitis	
	Flatulence		***Flatulence (Gr 2)***
	Gastritis		***Gastritis (Gr 2)***
	Gastroesophageal reflux disease		
		Gastrointestinal perforation[2]	
Mucositis oral			***Mucositis oral (Gr 3)***

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
		Pancreatitis	
Rectal mucositis			***Rectal mucositis (Gr 2)***
Small intestinal mucositis			***Small intestinal mucositis (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Flu like symptoms		
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
HEPATOBILIARY DISORDERS			
		Cholecystitis	
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (necrotizing fasciitis)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	CPK increased		
	Creatinine increased		***Creatinine increased (Gr 3)***
		Electrocardiogram QT corrected interval prolonged	
	Lipase increased		***Lipase increased (Gr 4)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Serum amylase increased		***Serum amylase increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperuricemia		***Hyperuricemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		
		Hypoglycemia	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
		Musculoskeletal and connective tissue disorder - Other (fistula formation)	
	Myalgia		***Myalgia (Gr 2)***
		Osteonecrosis of jaw	
	Pain in extremity		***Pain in extremity (Gr 2)***
		Rhabdomyolysis	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Leukoencephalopathy	
		Nervous system disorders - Other (cerebral infarction)	
	Paresthesia		
		Reversible posterior leukoencephalopathy syndrome	
		Transient ischemic attacks	
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Nephrotic syndrome	
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		***Epistaxis (Gr 2)***
Laryngeal mucositis			***Laryngeal mucositis (Gr 2)***
Pharyngeal mucositis			***Pharyngeal mucositis (Gr 2)***
Tracheal mucositis			***Tracheal mucositis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
	Hair color changes		***Hair color changes (Gr 2)***

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Pruritus		
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
		Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event	
	Vascular disorders - Other (hemorrhage)[4]		

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

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

[3]Allergic reactions observed include anaphylaxis and angioedema.

[4]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI tract, GU system, respiratory tract, nervous system [including fatal intracranial hemorrhage, and cerebrovascular accident], and tumor site) have been reported.

Adverse events reported on Sunitinib malate (SU011248 L-malate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Sunitinib malate (SU011248 L-malate) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Pericardial effusion
GASTROINTESTINAL DISORDERS - Ascites; Dysphagia; Gastrointestinal disorders - Other (enteritis); Hemorrhoids; Ileus; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Pain
INVESTIGATIONS - GGT increased; INR increased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Peripheral sensory neuropathy; Seizure; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion
RENAL AND URINARY DISORDERS - Hematuria; Urinary retention

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pharyngolaryngeal pain; Pleural effusion; Pneumothorax
VASCULAR DISORDERS - Flushing; Hypotension

Note: Sunitinib malate (SU011248 L-malate) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 CTEP Reporting Requirements

7.2.1 Adverse Event Characteristics

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

'Expectedness': AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1).

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

7.2.2 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions. AEs reported through CTEP-AERS must also be reported in routine study data submissions.

7.2.3 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (**Section 7.2.3**).

A 24-hour notification is to be made to CTEP by telephone at 301-897-7497 only when internet connectivity is disrupted. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS by the original submitter at the site.

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

7.2.4 Expedited Reporting Guidelines

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

IMPORTANT: Deaths clearly due to progressive disease should NOT be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

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

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.2.5 Protocol-Specific Expedited Adverse Event Reporting Exclusions

Lymphopenia (any grade), alopecia (any grade), anemia (grade 2), electrolytes (grade 2: sodium, potassium, phosphorous, and magnesium), albumin (grade 2), hyperuricemia (grade 3), INR (grade 2), and PTT (grade 2) will NOT be reported through CTEP-AERS but will be reported in the routine data submissions.

7.2.6 Multicenter Guidelines for Expedited Adverse Event Reporting

Adverse Event Reporting via CTEP-AERS:
Follow sponsor expedited AE reporting requirements in Section 7.2.4. Copy Ashley Bruns (ashley.bruns@nih.gov) and Alice Chen, MD (chenali@mail.nih.gov) on all CTEP-AERS reports.

Adverse Event Reporting to NIH IRB:
The site PI must immediately report to the Coordinating Center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 24 hours of PI awareness of the event. The site PI must also report any protocol deviations or violations to the Coordinating Center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

Follow NIH IRB expedited AE reporting requirements in Section 7.3. Complete the NIH IRB Expedited AE form supplied by the Coordinating Center. Send the completed form to Ashley Bruns, RN, either by e-mail to ashley.bruns@nih.gov or by fax to (301) 451-5625.

7.2.7 Secondary Malignancy

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

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

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

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

7.2.8 Second Malignancy

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

7.3 NIH IRB Reporting Requirements

7.3.1 Definitions

Please refer to definitions provided in Policy 801: Reporting Research Events (https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs).

7.3.2 OHSRP Office of Compliance and Training / IRB Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.3.3 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs

7.3.4 NCI Clinical Director Reporting

Problems expeditiously reported to the OHSRP/IRB in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to the Clinical Director/designee at NCICCRQA@mail.nih.gov within one business day of learning of the death.

8 PHARMACEUTICAL INFORMATION

8.1 Cediranib (NSC 732208)

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

Other Names: AZD2171, AZD2171 maleate, Recentin™

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

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

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

Mode of Action: Cediranib 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.

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

In addition to the active ingredient, the tablets contain mannitol, dibasic calcium phosphate anhydrous, sodium starch glycollate, microcrystalline cellulose, and magnesium stearate with a

film coat coating hypromellose 2910 polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide.

Storage: The intact bottles should be stored at controlled room temperature (68-77°F) and protected from light.

Stability: Stability studies are ongoing.

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

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

In vitro studies using hepatic cultures show that cediranib (AZD2171) did not inhibit CYP 1A2, 2A6, 2C8, 2C9, 2C19 and 2E1 and showed no induction of CYP 1A2, 2B6 and 3A4/5. It did weakly inhibit CYP 2D6 and 3A4/5, but this inhibition not expected to cause any clinically relevant drug interactions. The possibility that cediranib (AZD2171) may induce gastrointestinal CYP3A and UGT enzymes cannot be excluded; therefore the efficacy of hormonal contraceptives may be reduced. Advise women study participants to use an additional non-hormonal contraceptive method.

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

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

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

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

Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for at least 6 weeks after the last dose of cediranib (AZD2171). Refer to the protocol document for specific guidance.
AZD2171 is provided to the NCI under a Clinical Trials Agreement (CTA) between AstraZeneca International (the Pharmaceutical Collaborator) and the DCTD, NCI (see Section 12.4).

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

8.2 Sunitinib Malate (NSC 736511)

Chemical Name: *N*-[2-(Diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide, compound with (S)-2- hydroxybutanedioic acid

Other Names: SU011248 L-malate, Sutent

Classification: Multi-kinase inhibitor

Molecular Formula: $C_{22}H_{27}FN_4O_2 \bullet C_4H_6O_5$

Molecular Weight: 532.57 Daltons

Mode of Action: Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib is an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET).

Description: Sunitinib malate is the L-malate salt of SU011248 free base.

How Supplied: Sunitinib malate capsules are supplied by Pfizer, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Capsules are packaged in 28-count bottles with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients in the following strengths:

- 12.5 mg hard gelatin capsule (size 4) with orange cap and orange body, printed with white ink "Pfizer" on the cap and "STN 12.5 mg" on the body.

- 25 mg hard gelatin capsule (size 3) with caramel cap and orange body, printed with white ink "Pfizer" on the cap and "STN 25 mg" on the body.

Orange gelatin capsule shells contain titanium dioxide, and red iron oxide. Caramel gelatin capsule shells contain titanium dioxide, red iron oxide, yellow iron oxide, and black iron oxide. White printing ink contains shellac, propylene glycol, sodium hydroxide, povidone, and titanium dioxide.

Storage: Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Stability: Refer to the package label for expiration.

Route of Administration: Oral administration, take with or without food.

Potential Drug Interactions: Sunitinib is metabolized primarily by CYP3A4. Avoid co-administration of strong CYP3A4 inducers/inhibitors.

Availability: Sunitinib malate is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Sunitinib malate is provided to the NCI under a Collaborative Agreement between Pfizer and the DCTD, NCI (see Section 12.4)

8.3 Agent Ordering and Agent Accountability

Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

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

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

ordering investigator on this protocol.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov

PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET).

9 CORRELATIVE STUDIES

With Amendment H (version dated 11/20/2013), biopsies will no longer be performed as part of this study. Language referencing biopsy collection has been left in the protocol for historical reference purposes.

Optional tumor biopsies will be collected from patients enrolled at the Clinical Center, NCI only for use in gene expression profiling studies, and for future analyses once more information is available from ongoing studies regarding the underlying mechanism of action of these agents in ASPS. When appropriate analyses are identified, the proposed correlative studies for the flash-frozen tumor samples will be submitted to the IRB for approval.

9.1 Laboratory Contact

At least 24 hours prior to taking the biopsies, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail (preferred): NCIPK-PDsupportgroup@mail.nih.gov; Pager (preferred): 102-12798; Phone: (240) 858-3963; Fax: (301) 480-5871. Tubes pre-labeled with the participant ID, biopsy date, protocol #, and site of tissue biopsy will be provided for tumor biopsy collection.

9.2 Timing of Biopsies

Biopsies will be performed at the following times from patients enrolled at the Clinical Center, NCI only:

- Before starting treatment on study (baseline)
- Between day 3 and day 5 of cycle 1 (Part I only)

The time point for the second biopsy has been selected to maximize the possibility that any transcriptional changes seen are due to a direct drug mechanism of action versus any inflammatory infiltrate- or other endpoint-related findings. The timing of the post-treatment biopsy may be adjusted depending on initial gene expression profile results, but the total number of biopsies per patient will not change.

9.3 Biopsy Procedure

Serial tumor biopsies will be obtained through Interventional Radiology by a percutaneous approach. For tumor biopsy site other than lung, 2 to 3 cores 18-gauge in diameter and at least 1 cm in length will be obtained at each time point. One core will be preserved in RNAlater for gene expression profiling; any additional cores will be flash frozen and kept for future analysis. For lung as site of tumor biopsy, only a fine needle aspiration (FNA) sample will be acquired and preserved in RNAlater for gene expression profiling.

It is estimated that there will be between 2-5 million cells from each biopsy. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and Interventional Radiology, an attempt at biopsy will be made. Determination of a disease site amenable to biopsy will be determined on an individual case basis after discussion with an interventional radiologist. The biopsy procedure to be used in this protocol is described below; local anesthesia will be administered. Such biopsies can be safely performed as evidenced by literature reports (Dowlati *et al*., 2001) as well as our experience at the Clinical Center. Risks of the procedure include, but are not limited to, bleeding, infection, pain, and scarring. We will follow Clinical Center Interventional Radiology SOPs for coagulant panel and platelets.

- All biopsies will be by percutaneous approach
- No biopsy by an invasive (endoscopic, laparoscopic, or surgical) procedure will be performed.
- Only cutaneous, subcutaneous, or easily accessible parenchymal lesion core biopsies will be performed.
- However, there will be no core biopsies of lung lesions. Only FNA of a lung lesion may be performed at the discretion of the PI after discussion with an interventional radiologist.

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team and may include ultrasound, CT scan, or MRI. Should CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. All cases will be carefully reviewed with the interventional

radiologists at NIH who have extensive experience in performing such procedures. Only if the procedure is considered to be low risk will we proceed with tumor biopsy in a given participant.

Tumor biopsies are optional. Baseline biopsies will be performed following patient enrolling on study. If an initial attempt at percutaneous biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt at percutaneous biopsy. A separate consent form must be signed for each biopsy procedure, so patients may choose not to undergo subsequent biopsies. If the baseline biopsy is unsuccessful or the patient chooses not to undergo subsequent biopsies, no further biopsies will be performed but the patient will remain on study and receive study medication.

9.4 Processing of Patient Tumor Samples For RNA Analysis

9.4.1 Biopsy Sample Collection and Storage

- Biopsy samples will be collected in 2.0 mL eppendorf tubes (RNAse and DNAse free, sterile) filled with RNAlater RNA Stabilization Reagent (# 76106 Qiagen) and sealed with parafilm. (Before use, check for RNAlater precipitate in tubes: in the unlikely event it is present, heat tubes at 37ºC and agitate until completely dissolved).
- Maintain tubes upright.
- Samples collected in the RNAlater can be held/stored at 4ºC OR room temperature until being shipped (within 48 h).

Ship via courier to:

Curtis Hose/Anne Monks
Functional Genomics Lab
DTP, National Cancer Institute at Frederick
Bldg. 432, Room 232
Frederick, Maryland 21702
Tel: (301)-846-1033 or 5528
Fax: (301)-846-6081

Confirm time of courier pick-up to: hosec@mail.nih.gov and monksa@mail.nih.gov.

9.4.2 Sample Analysis

Samples will be disrupted by FastPrep in RNA lysis buffer provided from Qiagen (RNeasy mini kit, #74106), and RNA will be extracted according to manufacturer's procedure.

100 ng of high quality RNA (Agilent RIN > 7) will be utilized for transcription profiling on Affymetrix U133 plus2 arrays, according to their protocols. The .cel files will be analyzed by Partek and Gene Sifter, for evaluation of individual drug-modulated genes and impact on pathways.

9.5 Processing of Frozen Tumor Samples

Biopsy samples will be transferred into a 1.5-mL pre-chilled cryovial prelabeled with a Unique Identifier Code for the specimen per NCTVL SOP340507, and the vial with the specimen will be immediately dropped into liquid nitrogen. Frozen specimens will be transported on dry ice by Clinical Service Program courier to the PADIS lab at FNLCR, where they will be logged into the record keeping system and stored in Dr. Robert Kinders' laboratory for future analysis.

Robert J. Kinders, PhD
Principal Scientist
PADIS, LHTP
Applied/Developmental Research Directorate
Leidos Biomed/FNLCR
Bldg 431, Rm 129
Frederick, MD 21702-1201
Tel: 301-846-6410

9.6 Sample Collection and Processing

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers. Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be sent for analysis and/or storage. Specimen labels will indicate: protocol number, order in which the patient enrolled on the trial, type of sample, collection time, and total volume collected, as appropriate.

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Any new use of these samples will require prospective IRB review and approval; any loss or destruction of samples and the planned disposition of samples after the protocol is terminated will be reported to the IRB.

10 STUDY CALENDAR

Eligibility screening evaluations are to be conducted within 8 days prior to enrollment, with the exception of informed consent, echocardiogram and diagnostic imaging, which must be done within 28 days prior to enrollment. Baseline history, physical examination, laboratory evaluations, and EKG are to be conducted within 8 days prior to the start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations, values from the screening evaluations may be used as baseline measurements; if > 8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, and EKG must be repeated prior to starting protocol therapy. Baseline imaging scans and echocardiogram scans must be done within 28 days prior to the start of protocol therapy. Start of next cycle may be changed by 1 day or delayed for up to 1 week to accommodate scheduling conflicts. The calendar restarts at Cycle 1 when patients start treatment on Part II. The research team may perform additional safety/monitoring tests as clinically indicated.

	Pre-Study Eligibility Screening	C1				C2				C3 on	Washout /Pre-Part II[a]	Off Tx
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9		
Cediranib OR sunitinib[a]		X	X	X	X	X	X	X	X	X		
Informed consent	X											
Demographics	X											
Medical history	X	X[l]										
Concurrent meds	X	X----------										X
Physical exam/vital signs/weight/ performance status[b]	X	X[l]		X		X				X	X	X
EKG[c]	X	X[l]				X				X	X	
Height	X											
Serum chemistry[d]	X	X[l]		X		X		X		X	X	X
CBC w/diff, plts[d]	X	X[l]		X		X		X		X	X	X
B-HCG[e]	X										X	
Tumor measurements[f]	X	X[l]	Tumor measurements are repeated every 2 cycles*									X
Urine dipstick or urinalysis for protein[g]	X	X[l]				X				X	X	X
Echo[h]	X	X[l]									X	
Adverse event evaluation		X ----------										X
TSH, T3, and T4[i]	X									X [i]	X	X
Troponin T or I[j]	X											
PK Evaluation[k]	X			X		X				X		

a: Cediranib (30 mg) OR sunitinib malate (37.5 mg) orally, once a day in 28-day cycles. At the time of disease progression, patients will cross over to the other treatment arm after a 2-week wash-out period, provided the other arm has not been closed due to inadequate activity (as defined in Section 13) or unacceptable toxicity. Eligibility tests will be repeated within 1 week prior to patients starting on Part II. The calendar restarts at Cycle 1 when patients start treatment on Part II.

b: BP monitoring by a health care provider should be performed every 2 weeks during cycle 1 of Part I and Part II and then at the beginning of subsequent cycles (every 3 cycles for patients on study for 2 years or longer). Patients should measure and record their blood pressure at home at least once per day for the duration of the study. History and physical exam will be done at the start of each cycle (every 3 cycles for patients on study for 2 years or longer) (up to 3 days before start of new cycle)

c: For eligibility screening and at baseline (within 8 days prior to enrolling or starting study drug, respectively), prior to patients starting on Part II, at the start of every cycle (every 3 cycles for patients on study for 2 years or longer), and as clinically indicated.

d: CBC (WBC, Hgb, Hct, platelets, ANC, % neutrophils, bands, lymphocytes) and serum chemistry (albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, glucose, magnesium, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium) every 2 weeks for the first 2 cycles of Part I and Part II, and then at the start of each cycle (every 3 cycles for patients on study for 2 years or longer) (up to 3 days before start of new cycle).

e: Urine pregnancy test (women of childbearing potential) for eligibility screening and prior to starting on Part II.

f: Appropriate anatomic imaging studies will be done for eligibility screening and at baseline (within 28 days prior to enrollment or starting study drug, respectively), and repeat imaging scans will be performed every 2 cycles (*every 3 cycles for patients on study for 2 years or longer). Documentation (radiologic) must be provided at time of crossover and during Part II if a patient is removed from study for progressive disease.

g: Evaluation of urine protein should occur for eligibility screening and at baseline (within 8 days prior to enrolling or starting study drug, respectively), and at the start of every cycle (every 3 cycles for patients on study for 2 years or longer) (up to 3 days before start of new cycle) if not previously abnormal (defined as ≥ 1+). If patient has significant proteinuria (>1+), obtain a 24 hour urine for protein and creatinine clearance.

h: ECHO will be obtained for eligibility screening and at baseline (within 28 days prior to enrolling or starting study drug, respectively) and prior to patients starting on Part II; if abnormal it will be repeated every 2 cycles. ECHO will be performed every other cycle of treatment in the following groups of patients: (1) those entering the trial with NYHA Class II cardiac dysfunction (see Appendix B), (2) those with a history of Class II heart failure who are asymptomatic on treatment, and (3) in those previously exposed to anthracyclines or thoracic irradiation if the heart was included in the radiotherapy port.

i: TSH every 2 cycles. T3, T4 as clinically indicated

j: Troponin T or troponin I will be measured for eligibility and as clinically indicated for patients receiving cediranib.

k: Blood samples for PK analyses of Cediranib will be collected in 4 cc EDTA (purple top) tubes pre-dose , and at the following time points prior to drug administration on that day: **cycle 1 day 15, C2D1, C3D1, and C4D1**. One 4 cc EDTA (purple top) tube will be obtained for each time point.

l: Eligibility screening results may be used for these baseline measurements if conducted within 8 days (for medical history, physical exam, EKG, serum chemistry, CBC, and urinalysis) or 28 days (for echo and tumor measurements) prior to the start of protocol therapy.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 2 cycles (8 weeks) or every 3 cycles for patients on study for 2 years or longer. Response and progression will be evaluated in this study using the original international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1) [Therasse et al. 2000]. Changes in the largest diameter (unidimensional measurement) of the

tumor lesions are used in RECIST 1. All radiographic studies will undergo an independent review to confirm the presence of objective responses.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with cediranib or sunitinib.

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

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

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by conventional techniques (CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or <10 mm using spiral CT scan) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will

be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response. A previously irradiated lesion can be considered a target lesion if it shows clear evidence of disease progression.
Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement.

Ultrasound When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated

equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

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

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

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

Progressive Disease (PD): At least a 20% increase in the sum of the LD of the target lesions, taking as reference the smallest sum on study of the LD recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the LD since the treatment started.

11.1.4.2 Evaluation of Non-Target Lesions

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

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

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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

11.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

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

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.

12.1 Data Reporting

12.1.1 Method

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

Note: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via the monitoring method identified above.

12.1.2 Responsibility for Submission

Study participants are responsible for submitting CDUS data and/or data forms to the Coordinating Center quarterly to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.1.1). The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 Data Safety and Monitoring Plan

The investigators at each participating center will be responsible for the collection, maintenance, and quality control of the study data. Adverse events observed in patients enrolled on the trial will be monitored in real time by the Principal and Associate Investigators, and attribution of these events to the research will be determined at the end of each treatment cycle in each subject. The clinical research team (PI, adjunct PI, research nurses, data managers) will meet weekly when patients are being actively treated on the trial to discuss each patient in detail and ensure that all events are graded appropriately, and that the attribution to study drug is correct. The Coordinating Center is responsible for establishing conference calls between participating sites to discuss the observed toxicities and protocol issues at least on a monthly basis.

All SAEs will be reported through CTEP-AERS to CTEP, to the Coordinating Center PI at NCI, and forwarded to the IRB per Section 7. In all cases where the dose of the study treatment has been reduced/modified or the patient withdrawn due to unusual or unusually severe toxicity considered related to the study treatment, the investigator must contact and inform the Coordinating Center PI. All sites will be monitored by the CTEP drug monitor who will receive data from all participating sites.

Data will be monitored regularly by the PI to identify significant toxicity trends. Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients.

Confidentiality will be maintained as much as possible, consistent with applicable regulations. Names of participants or identifying material will not be released without patient permission, except when such release is required by law. No patient's name or identifying information will be released in any publication or presentation. Records are maintained according to current legal requirements, and are made available for review according to the requirements of the FDA or other authorized user, only under guidelines established by the Federal Privacy Act.

Safety Monitoring Committee:
Because this is a multi-institutional protocol for which the NCI CCR is the coordinating center, it will be monitored by the NCI Safety Monitoring Committee (SMC).

12.3 Multicenter Guidelines

This protocol will open initially at the NCI. The NIH IRB will be notified once the participating centers' IRBs have approved the studies to open. This protocol will follow the CCR's Clinical Research Operations' SOPs for multicenter trials.

12.3.1 IRB Approvals

As the Coordinating Center for a trial, it is the PI's responsibility to ascertain that no patients are entered on the trial at a participating institution without full IRB approval. Thus, the NIH IRB must approve the addition of each participating institution to the protocol and will require a copy of the local IRB approval from each participating institution before NIH IRB approval will be granted.

The PI will provide the NIH IRB with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NIH IRB.

12.3.2 Amendments and Consents

The NCI PI will provide the NIH IRB with copies of all amendments, consent forms, and approvals from each participating institution.

12.3.3 Data Collection

The investigators will be responsible for the collection, maintenance, and quality control of the study data. All data collected for each study subject will be entered into the Cancer Central Clinical Database (C3D), an NCI electronic case report form/database, every 2 weeks. The participating sites will be able to enter the data remotely into the web-based C3D system. Each site investigator is also responsible for maintaining all source documentation related to the study, including any films, tracings, computer discs or tapes. NCI will be responsible for data management, data analysis, and reporting. Data collection forms will be provided to the

participating institutions. Required data include, not exclusively: prior disease-related therapies with dates, disease type, stage, disease sites, with measurements, and concurrent medications.

12.3.4 Data and Center Audits

Audits will be conducted yearly to ensure data integrity and provide quality control. These audits will be conducted by the NCI research team. Selected patient charts should be audited as well as the participating institution's Standard Operating Procedures (SOP) at the time of the visit. Data from participating institutions should be available when the protocol is audited at the NCI.

12.3.5 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix K.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

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

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

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

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

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

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

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

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

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that

Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to: E-mail: ncicteppubs@mail.nih.gov

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

12.5 Publication Policy

Recognizing the need to make clinical trial outcomes rapidly available to the cancer clinical trials community (Doroshow, 2008), publication of the results from this study will be a priority following completion of accrual, follow up, and data analyses.

Authorship of this group-wide study will include the Coordinating Center PI, the study statistician, and one representative from each participating institution listed on the cover page of the protocol that contributed more than 10% of the eligible, evaluable cases. The first author, last author, corresponding author(s), and study statistician, will all be NCI investigators. The CTEP medical monitor will also be listed as an author. Lead investigators from laboratories involved in conducting correlative studies will be listed as authors if data from their laboratories are included in the clinical results manuscript.

If several investigators were responsible for a participating institution's accrual, the designated representative from that institution ordinarily will be the PI. When an individual other than the PI is largely responsible for a participating institution's accrual, the PI is expected to substitute that individual as an author in place of himself/herself. The intent is to offer recognition to the individuals who have been most directly involved in the study. Because the Coordinating Center PI will often be unaware of the relative contributions of investigators at each institution, the PIs at participating institutions accruing more than 10% of cases will be solicited routinely to determine whether another individual should be substituted for them in authorship. There will be only one author from each of the participating institutions listed on the cover page of the protocol. If the PI is already an author, based on scientific contribution to the study, a second person from that PI's institution will not automatically be accepted for authorship based on institutional accrual.

This protocol includes several correlative studies that may be published with the group-wide clinical results paper or as separate, stand-alone scientific papers. The decision to publish correlative study papers separately will be made by the Coordinating Center PI and relevant correlative study investigators, and will be subject to the Collaborative Agreement for study publications described in Section 12.4. Authorship of the correlative results paper will include the Coordinating Center PI, the correlative study lead investigators, and researchers from the

correlative studies laboratories nominated by the correlative study lead investigators. Correlative study lead investigators may also nominate authors who have contributed to the feasibility of the study and/or the development of assays and procedures that supported evaluation of study samples. The final decision on the authorship of any manuscripts related to this trial will be made by the Coordinating Center PI.

13 STATISTICAL CONSIDERATIONS

Patients enrolled after Amendment G (version dated 08/16/2013), will be evaluated and compared to the first 13 patients by the study statistician and the Principal Investigator. PFS at 24 weeks will be calculated for all the study participants and for the initial 13 patients and rest of the patients separately to assess for any differences. Patients with newly diagnosed ASPS and clinical evidence of disease progression will also be assessed separately.

The primary objective of this study is to determine whether either sunitinib or cediranib can be associated with a modest rate of clinical response in patients with ASPS. In addition, it will be of interest to obtain estimates of the PFS for each agent separately, as well as estimates of the response rate and the PFS for each agent when administered after patients progress on their initial agent.

For patients who are not newly diagnosed:

In each of the two arms, which are randomized against one another to prevent bias in patient selection only, the study will be conducted as an optimal two-stage phase II trial (Simon, 1989) to rule out an unacceptably low 15% clinical response rate (PR+CR; p0=0.15) in favor of a modestly high response rate of 40% (p1=0.40). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), the study will initially enroll 10 evaluable patients in each arm. If 0 or 1 of the 10 patients has a clinical response, then no further patients will be accrued. That treatment arm will be closed to the accrual of new patients, and there will be no crossover of patients who progressed on the other agent to the closed arm. If 2 or more of the first 10 patients have a response, then accrual would continue until a total of 22 patients have enrolled in that arm. As it may take several weeks to determine whether a patient has experienced a clinical response, a temporary pause in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 2-5 responses in 22 patients, this would be an uninterestingly low response rate in that arm, while if there were 6 or more responses in 22 patients, then this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (15% response rate), the probability of early termination is 54% for each arm.

There will be no formal comparison of the response rates obtained on the two arms as this is not the purpose of the study and the trial does not have sufficient power to detect any reasonable difference between the arms. Treatment in this trial is open label, and there will be no comparisons to placebo. The response rates and 90% and 95% confidence intervals will be presented. If accrual ends to one arm because of lack of adequate responses in the first stage, the

other arm will remain open to accrue all necessary patients. The PFS will be estimated based on the 22 evaluable patients randomized to each treatment. The 4- and 6-month estimates will be formed, and reported with 90% and 95% confidence intervals, as well as presenting the Kaplan-Meier curve for PFS. In addition, once patients progress on their initially assigned therapy, the response rate for the second therapy will be determined as well as the corresponding 90% and 95% confidence intervals. The PFS will also be determined from the date of progression for patients upon crossing over to the other agent. At the end of the study we will also analyze for the best response in two stages, and the time to final disease progression following treatment with both agents for the two arms, at 24 weeks.

Following Amendment K (8/26/14), patients with newly diagnosed ASPS will be accrued and assessed separately using their own individual two-stage designs as follows:

In each of the two arms of the newly diagnosed ASPS cohort, which are randomized against one another to prevent bias in patient selection only, the study will be conducted as a Minimax two-stage phase II trial (Simon, 1989) to rule out an unacceptably low 15% clinical response rate (PR+CR; p0=0.15) in favor of a modestly high response rate of 45% (p1=0.45). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.20 (probability of rejecting a good treatment=0.20), the study will initially enroll 8 evaluable newly diagnosed patients in each arm. If 0 or 1 of the 8 patients has a clinical response, then no further newly diagnosed patients will be accrued to that arm. That treatment arm will be closed to the accrual of new patients, and there will be no crossover of patients who progressed on the other agent to the closed arm. If 2 or more of the first 8 patients have a response, then accrual would continue until a total of 11 patients have enrolled in that arm. As it may take several weeks to determine whether a patient has experienced a clinical response, a temporary pause in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 2-3 responses in 11 patients, this would be an uninterestingly low response rate in that arm, while if there were 4 or more responses in 11 patients, then this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (15% response rate), the probability of early termination is 66% for each arm.

If a treatment arm is closed due to inadequate activity, as defined above, or unacceptable toxicity, patients will not be eligible to cross over to that arm. As of Amendment Y (dated May 6, 2019), we have closed the cediranib arm of the newly diagnosed ASPS cohort due to inadequate activity (1 PR out of 8 evaluable patients). All newly diagnosed ASPS patients will be assigned to the sunitinib malate treatment arm; they will not cross over to the cediranib treatment arm.

13.1 Sample Size/Accrual Rate

With an anticipated accrual of 14-16 patients per year, it is expected that 4-5 years will be required to enroll 44 evaluable non-newly diagnosed and 22 newly diagnosed patients. To allow for a small number of inevaluable patients, the accrual ceiling will be set at 70.

14 HUMAN SUBJECTS PROTECTION

14.1 Rationale for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. For safety reasons, pregnant women and children age <16 years are excluded from this study. The NCI is the coordinating center for this multi-institutional study. This study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer.) Participants should realize that there is no guarantee of benefit to them from participation in this trial. The results of this trial may benefit future cancer patients. To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

Inclusion of Women and Minorities:
This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. The table below includes accrual estimates for the duration of the study.

14.2 Justification for Exclusions

Pregnant women are excluded from this study because sunitinib and cediranib are VEGF inhibitors with known abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with these agents, breastfeeding should be discontinued. Participants with unstable or serious medical conditions such as uncontrolled diabetes, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements are excluded due to the possibility that the underlying condition may obscure the attribution of effect and adverse events and may limit study compliance. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with cediranib. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

14.3 Participation of Children

This study includes patients 16 years of age and older. Because insufficient dosing or adverse event data are currently available on the use of cediranib in patients <16 years of age, children are excluded from this study, but may be eligible for future pediatric trials. Studies will be performed in patients <16 years of age when it is appropriate to do so.

14.4 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Section 5. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

14.5 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients (and the parents of patients aged 16 or 17) of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient (and the parents of patients aged 16 or 17) will be provided an IRB-approved consent for review and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient (or, in the case of patients aged 16 or 17, written assent from the patient and written consent from the patient's parent will both be documented). The original signed consent goes to Medical Records; a copy will be placed in the research record. Patients will not be consented by telephone.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

The investigators are requesting a waiver from the IRB to allow only one parent to sign the informed consent to enter a child on the protocol. Because many patients must travel to the NIH from long distances at substantial expense, requiring both parents to be present for the consent process could be a financial hardship for many families. When guardianship status of the child is uncertain, documentation of custody status must be obtained. In situations where there is joint custody of a child, both parents must sign consent. If only one parent can be present at NIH, the other parent's consent can be obtained by telephone.

14.5.1 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require re-consenting of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. Given the length of time that has transpired for some of the subjects since their last visit for this study, we request waiver of informed consent for those individuals who have completed their participation in the research study or who become lost to follow up during their participation in the research study.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.

a. Analysis of samples and data from this study involves no additional risks to subjects.

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.
(3) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.
(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
    a. We only plan to request a waiver of reconsent for those subjects who have been lost to follow-up or who, prior to the approval of Amendment T, have been taken off study before reaching the age of majority.

14.5.2 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (*i.e.*, long-term stabilization and/or improvement in the pain and physical impairment caused by ASPS; **Section 14.4**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH OHSRP Policy 403 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

14.6 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication. This research represents a greater than minimal risk to participants, but presents the prospect of direct benefit to individual subjects.

For patients enrolled at the Clinical Center, NCI only, the research component of this study required to obtain 2 CT tumor biopsies confers radiation exposure at an effective dose of 0.29 rem. This dose is below NIH RSC guidelines and represents a slightly greater than minimal risk to patients. *With Amendment H (version dated 11/20/2013), research biopsies will no longer be performed as part of this study.*

14.6.1 Patient Advocate

The patients' rights representative is available to patients receiving treatment on this protocol at the NIH Clinical Center at (301) 496-2626 in Building 10 of the Clinical Research Center, Room 1-3521, on the Bethesda NIH campus. Patients enrolled at other sites will be given information regarding their local patient advocate. Patients will be informed that they can contact the study PI or RN at any time with questions about their medical care, and that the patients' rights representative is also available to answer non-medical questions about the study.

REFERENCES

Alberts, S.R., B.W. Morlan, G.P. Kim, *et al*. NCCTG phase II trial (N044J) of AZD2171 for patients with hepatocellular carcinoma (HCC)-interim review of toxicity. J Clin Oncol 2007; 25:A186.

American Cancer Society. Cancer Facts and Figures 2010. Atlanta: American Cancer Society; 2010.

Anderson ME, Hornicek FJ, Gebhardt MC, Raskin KA, Mankin HJ. Alveolar soft part sarcoma: a rare and enigmatic entity. Clin Orthop Relat Res 2005;438: 144-8.

AstraZeneca. Investigator's Brochure: Cediranib, AZD2171, RECENTIN™, Edition 14. November 2009.

Azizi AA, Haberler C, Czech T*, et al.* Vascular-endothelial-growth-factor (VEGF) expression and possible response to angiogenesis inhibitor bevacizumab in metastatic alveolar soft part sarcoma. Lancet Oncol 2006;7: 521-3.

Batchelor T, Sorensen G, di Tomaso E*, et al.* A multidisciplinary phase II study of AZD2171 (cediranib), an oral pan-VEGF receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. AACR Meeting Abstracts 2008; LB-247.

Batchelor T, Mulholland P, Neyns B, *et al*. A phase III randomized study comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, with lomustine alone in recurrent glioblastoma patients. Ann Oncol 2010:21(Suppl 8):viii4, abstract LBA7.

Bello, C., B. Houk, L. Sherman, *et al*. Effect of rifampin on the pharmacokinetics of SU11248 in healthy volunteers. ASCO Meeting Abstracts 2005; 23:A3078.

Bello, C.L., L. Sherman, J. Zhou, *et al*. Effect of food on the pharmacokinetics of sunitinib malate (SU11248), a multi-targeted receptor tyrosine kinase inhibitor: Results from a phase I study in healthy subjects. Anticancer Drugs 2006; 17:353-358.

Bisogno G, Rosolen A, Carli M. Interferon alpha for alveolar soft part sarcoma. Pediatr Blood Cancer 2005;44: 687-8.

Brell J.M., J.A. Bokar, M.M. Cooney, *et al.* Phase I study of sunitinib malate continuously dosed and standard-infusion gemcitabine in solid tumors. ASCO Meeting Abstracts 2008; 26:A13533

Brennan MF, Alektiar KM, Maki RG. Sarcomas of the soft tissue and bone. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer, principles and practice of oncology. 6th ed. Philadelphia: Lippincott, Williams & Wilkins; 2001. p. 1841-91.

Britten, C.D., F. Kabbinavar, J.R. Hecht, *et al*. A phase I and pharmacokinetic study of sunitinib administered daily for 2 weeks, followed by a 1-week off period. Cancer Chemother Pharmacol 2008; 61:515-524.

Burstein HJ, Elias AD, Rugo HS*, et al.* Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2008;26:1810-6.

Casanova M, Ferrari A, Bisogno G*, et al.* Alveolar soft part sarcoma in children and adolescents: A report from the Soft-Tissue Sarcoma Italian Cooperative Group. Ann Oncol 2000;11:1445-9.

Chan KR, Gundala S, Laudadio M, Mastrangelo M, Yamamoto A, Sato T. A pilot study using sunitinib malate as therapy in patients with stage IV uveal melanoma. J Clin Oncol 2008;26:9047.

Chaskis C, Sadones J, Michotte A, Dujardin M, Everaert H, Neyns B. A phase II trial of sunitinib in patients with recurrent high-grade glioma. J Clin Oncol 2008;26:13001.

Chi, A.S., E.R. Gerstner, A.F. Eichler, *et al*. Phase Ib study of cediranib in combination with temozolomide and radiation in patients with newly diagnosed glioblastoma. J Clin Oncol 2009; 27:A13010.

Chiorean E.G., C.J. Sweeney, C.F. Verschraegen *et al.* Tolerability/safety of sunitinib (SU) on schedule 2/1 in combination with capecitabine (C) in patients with advanced solid tumors. J Clin Oncol 2008; 26:A3562.

Choong NW, Cohen EE, Kozloff MF*, et al.* Phase II trial of sunitinib in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). J Clin Oncol 2008;26:6064.

Chow, L.Q., and S.G. Eckhardt. Sunitinib: from rational design to clinical efficacy. J Clin Oncol 2007; 25:884-96

Chow, L. Q., D.L. Yonker, S.A. Laurie, *et al.* Sunitinib (SU) in combination with pemetrexed (P) in patients (pts) with advanced solid malignancies: a phase I dose escalation study. J Clin Oncol 2008; 26:A3566.

Chu TF, Rupnick MA, Kerkela R*, et al.* Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370: 2011-9.

Cohen EE, Needles BM, Cullen KJ*, et al.* Phase 2 study of sunitinib in refractory thyroid cancer. J Clin Oncol 2008;26:A6025.

Cooney, M.M., J.A. Garcia, P. Elson, *et al.* Sunitinib and bevacizumab in advanced solid tumors: a phase I trial. J Clin Oncol 2008; 26:A3530.

Cunningham D, Wong RP, D'haens G*, et al.* A phase II, double-blind, randomized multicenter study of cediranib with FOLFOX versus bevacizumab with FOLFOX in patients with previously treated metastatic colorectal cancer (mCRC): Final PFS results. J Clin Oncol 2008;26:A4028.

Daigeler A, Kuhnen C, Hauser J*, et al.* Alveolar soft part sarcoma: clinicopathological findings in a series of 11 cases. World J Surg Oncol 2008;6:71.

Demetri GD, Desai J, Fletcher JA*, et al.* SU11248, a multi-targeted tyrosine kinase inhibitor, can overcome imatinib (IM) resistance caused by diverse genomic mechanisms in patients (pts) with metastatic gastrointestinal stromal tumor (GIST). J Clin Oncol 2004;22: 3001.

Demetri GD, van Oosterom AT, Garrett CR*, et al.* Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-38.

Denduluri, N., A.W. Berman, U. Vatas, *et al*. Cardiotoxicity after doxorubicin and AZD2171, an oral vascular endothelial growth factor receptor (VEGFR) inhibitor, in patients (pts) with breast cancer. J Clin Oncol 2007; 25:A554.

Desai J, Maki R, Heinrich MC*, et al.* Activity and tolerability of the multi-targeted tyrosine kinase inhibitor SU011248 in patients (pts) with metastatic gastrointestinal stromal tumor (GIST) refractory to imatinib mesylate. Proc Am Soc Clin Oncol Gastrointestinal Cancers Symposium 2004: A7.

Desai J, Yassa L, Marqusee E*, et al.* Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med 2006;145:660-4.

Dileo, P., A.D. Van Den Abbeele, J. Manola, *et al*. Qualitative assessment of ^{18}FDG-PET correlates with clinical benefit in patients (pts) with imatinib mesylate (IM)-resistant GIST treated with the multi-targeted tyrosine kinase inhibitor SU11248. Proc Am Soc Clin Oncol Gastrointestinal Cancers Symposium 2005:A8.

Doroshow J.H. Commentary: publishing cancer clinical trial results: a scientific and ethical imperative. Oncologist 2008;13(9):930-932.

Dowlati, A., Haaga, J., Remick, S.C*., et al.* Sequential tumor biopsies in early phase clinical trials of anticancer agents for pharmacodynamic evaluation. Clin Cancer Res 2001;7: 2971-6.

Drevs J, Esser N, Wedge SR, Ryan AJ, Ogilvie DJ, Marme D. Effect of AZD2171, a highly potent VEGF receptor tyrosine kinase inhibitor, on primary tumor growth, metastasis and vessel density in murine renal cell carcinoma. AACR Meeting Abstracts 2004;A1051.

Drevs J, Siegert P, Medinger M*, et al.* Phase I Clinical Study of AZD2171, an Oral Vascular Endothelial Growth Factor Signaling Inhibitor, in Patients With Advanced Solid Tumors. J Clin Oncol 2007;25:3045-54.

DuBois, S.G., S. Shusterman, A.M. Ingle, *et al.* A pediatric phase I trial and pharmacokinetic (PK) study of sunitinib: A Children's Oncology Group Phase I Consortium study. J Clin Oncol 2008; A3561.

Faivre S, Delbaldo C, Vera K*, et al.* Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol 2006;24:25-35.

Faivre S, Demetri G, Sargent W, Raymond E. Molecular basis for sunitinib efficacy and future clinical development. Nat Rev Drug Discov 2007;6:734-45.

Feldman, D.R., M.S. Ginsberg, M. Baum, *et al.* Phase I trial of bevacizumab plus sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol 2008; 25:A5100.

Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9: 669-76.

Fiedler, W., H. Serve, H. Döhner, *et al*. A phase 1 study of SU11248 in the treatment of patients with refractory or resistant acute myeloid leukemia (AML) or not amenable to conventional therapy for the disease. Blood 2005; 105:986-993.

Fischer P., P. Patel, M.A. Carducci, *et al.* Phase I study combining treatment with temsirolimus and sunitinib malate in patients with advanced renal cell carcinoma. J Clin Oncol 2008; 26:A16020.

Gadgeel SM, Wozniak A, Edelman MJ*, et al.* Cediranib, a VEGF receptor 1, 2, and 3 inhibitor, and pemetrexed in patients (pts) with recurrent non-small cell lung cancer (NSCLC). J Clin Oncol 2009;27: A19007.

Gallagher DJ, Milowsky MI, Gerst SR*, et al.* Final results of a phase II study of sunitinib in patients (pts) with relapsed or refractory urothelial carcinoma (UC). J Clin Oncol 2008; 26:A5082-.

Gan HK, Seruga B, Knox JJ. Sunitinib in solid tumors. Expert Opin Investig Drugs 2009;18: 821-34.

Gardner K, Leahy M, Alvarez-Gutierrez M, Judson I, Scurr M. Activity of the VEGF/KIT tyrosine kinase inhibitor Cediranib (AZD 2171) in alveolar soft part sarcoma. Abstract # 34936. Connective Tissue Oncology Society 14th Annual Meeting. London, United Kingdom; 2008.

Gardner K, Judson I, Leahy M, et al. Activity of cediranib, a highly potent and selective VEGF signaling inhibitor, in alveolar soft part sarcoma. J Clin Oncol 2009;27:A10523.

Garland LL, Chansky K, Wozniak A, et al. SWOG S0509: A phase II study of novel oral antiangiogenic agent AZD2171 (NSC-732208) in malignant pleural mesothelioma. J Clin Oncol 2009;27:A7511.

George, D.J., G. Liu, G. Wilding, *et al.* Sunitinib in combination with docetaxel and prednisone in patients with metastatic hormone-refractory prostate cancer (mHRPC) - preliminary results. J Clin Oncol 2008; 26:A5131

Ghose A, Tariq Z, Veltri S. Treatment of Multidrug Resistant Advanced Alveolar Soft Part Sarcoma with Sunitinib. Am J Ther 2010; Publish Ahead of Print: 10.1097/MJT.0b013e3181e70d20.

Goodman VL, Rock EP, Dagher R*, et al.* Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. Clin Cancer Res 2007; 13:1367-73.

Goss G, Shepherd FA, Laurie S*, et al.* A phase I and pharmacokinetic study of daily oral cediranib, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer: A study of the National Cancer Institute of Canada Clinical Trials Group. Eur J Cancer 2009; 45:782-88.

Heath, E.I., G.R. Blumenschein, J.R. Cohen, *et al.* Phase I study of sunitinib in combination with carboplatin (C) plus paclitaxel (P) in patients (pts) with advanced solid tumors (STs). J Clin Oncol 2008; 26:A3565.

Hennequin LF, Thomas AP, Johnstone C*, et al.* Design and structure-activity relationship of a new class of potent VEGF receptor tyrosine kinase inhibitors. J Med Chem 1999;42:5369-89.

Herbst, R.S. Toxicities of antiangiogenic therapy in non-small cell lung cancer. Clin Lung Cancer 2006; 8(suppl 1): S23-S30.

Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 2005;23:1011-27.

Hirte HW, Vidal L, Fleming GF*, et al.* A phase II study of cediranib (AZD2171) in recurrent or persistent ovarian, peritoneal or fallopian tube cancer: Final results of a PMH, Chicago and California consortia trial. J Clin Oncol 2008;26:A5521.

Hoff PM, Hochhaus A, Pestalozzi BC, *et al*. Cediranib + FOLFOX/XELOX versus placebo + FOLFOX/XELOX in patients (pts) with previously untreated metastatic colorectal cancer (mCRC): a randomized, double-blind, Phase III study (HORIZON II). Ann Oncol 2010:21(Suppl 8):viii9, abstract LBA19.

Izzedine H, Buhaescu I, Rixe O, Deray G. Sunitinib malate. Cancer Chemother Pharmacol 2007;60: 357-64.

Jurgensmeier JM, Brave SR, James NH, Wedge SR, Ogilvie DJ, Barry ST. AZD2171, a highly potent inhibitor of VEGF receptor signaling, has additional activity versus the c-Kit receptor tyrosine kinase. AACR Meeting Abstracts 2005;2005:1373.

Kamba, T.,and D.M. McDonald, Mechanisms of adverse effects of anti-VEGF therapy for cancer. Br J Cancer 2007; 96:1788-1795.

Kappers,M.H.W., J.H.M. van Esch, S. Sleijfer, *et al*. Cardiovascular and renal toxicity during angiogenesis inhibition: Clinical and mechanistic aspects. J Hypertens 2009; 27:2297-2309.

Karakunnel JJ, Gulley JL, Arlen PM*, et al.* Phase II trial of cediranib (AZD2171) in docetaxel-resistant, castrate-resistant prostate cancer (CRPC). J Clin Oncol 2008;26:A5136.

Karakunnel JJ, Gulley JL, Arlen P*, et al.* Cediranib (AZD2171) in docetaxel-resistant, castration-resistant prostate cancer (CRPC). J Clin Oncol 2009;27:A5141.

Kayton ML, Meyers P, Wexler LH, Gerald WL, LaQuaglia MP. Clinical presentation, treatment, and outcome of alveolar soft part sarcoma in children, adolescents, and young adults. J Pediatr Surg 2006;41: 187-93.

Keohan ML, Morgan JA, D'Adamo DR*, et al.* Continuous daily dosing (CDD) of sunitinib (SU) in patients with metastatic soft tissue sarcomas (STS) other than GIST: Results of a phase II trial. J Clin Oncol 2008;26:A10533.

Khakoo AY, Kassiotis CM, Tannir N*, et al.* Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. Cancer 2008;112:2500-8.

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

Kulke MH, Lenz HJ, Meropol NJ*, et al.* Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol 2008;26:3403-10.

Kuriyama K, Todo S, Hibi S, Morimoto A, Imashuku S. Alveolar soft part sarcoma with lung metastases. Response to interferon alpha-2a? Med Pediatr Oncol 2001;37:482-3.

Langenberg, M.H.G., C.M.L. van Herpen, J. de Bono, *et al*. Effective strategies for management of hypertension after vascular endothelial growth factor signaling inhibition therapy: Results from a phase II randomized, factorial, double-blind study of cediranib in patients with advanced solid tumors. J Clin Oncol 2009; 36:6152-6159.

Launay-Vacher, V., and G. Deray. Hypertension and proteinuria: A class-effect of antiangiogenic therapies. Anticancer Drugs 2009; 20:81-82.

Laurie SA, Gauthier I, Arnold A*, et al.* Phase I and pharmacokinetic study of daily oral AZD2171, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with carboplatin and paclitaxel in patients with advanced non-small-cell lung cancer: the National Cancer Institute of Canada clinical trials group. J Clin Oncol 2008; 26:1871-8.

Lazar AJF, Das P, Tuvin D*, et al.* Angiogenesis-Promoting Gene Patterns in Alveolar Soft Part Sarcoma. Clinical Cancer Research 2007;13:7314-21.

Leong, S., S.G. Eckhardt, E. Chan, *et al.* A phase I study of sunitinib in combination with modified FOLFOX 6 (mFOLFOX6) chemotherapy. Proc Am Soc Clin Oncol Gastrointestinal Cancers Symposium 2007; A285.

Lieberman PH, Brennan MF, Kimmel M, Erlandson RA, Garin-Chesa P, Flehinger BY. Alveolar soft-part sarcoma. A clinico-pathologic study of half a century. Cancer 1989;63:1-13.

Lindsay CR, MacPherson IR, Cassidy J. Current status of cediranib: the rapid development of a novel anti-angiogenic therapy. Future Oncol 2009;5:421-32.

Mashkani B, Griffith R, Ashman LK. Colony stimulating factor-1 receptor as a target for small molecule inhibitors. Bioorg Med Chem 2010;18:1789-97.

Matulonis UA, Berlin ST, Krasner CN*, et al.* Cediranib (AZD2171) is an active agent in recurrent epithelial ovarian cancer. J Clin Oncol 2008; 26:A5501.

Matulonis UA, Berlin S, Ivy P*, et al.* Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. J Clin Oncol 2009;27:5601-6.

Mayer E, Hamel S, Savoie J, *et al*. AZD2171 for refractory breast cancer: a phase 2 trial. Breast Cancer Res Treat 2007; 106(suppl 1): S274.

Mena AC, Pulido EG, Guillen-Ponce C. Understanding the molecular-based mechanism of action of the tyrosine kinase inhibitor: sunitinib. Anticancer Drugs 2010;21 Suppl 1: S3-11.

Mendel DB, Laird AD, Xin X*, et al.* In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 2003;9: 327-37.

Michaelson, M.D., A. Schwarzber, D.P. Ryan, *et al.* A phase I dose-finding study of sunitinib (SU) in combination with gemcitabine (G) in patients with advanced solid tumors. J Clin Oncol 2008; 26:A14522.

Moehler, M., J. T. Hartmann , F. Lordick, *et al.* Sunitinib in patients with chemo-refractory metastatic gastric cancer: Preliminary results of an open-label, prospective nonrandomized multicenter Aio phase II trial. Proc Am Soc Clin Oncol Gastrointestinal Cancers Symposium 2009; A61.

Motzer, R.J., G. Hudes, G. Wilding, *et al.* Phase I trial of sunitinib malate plus interferon-α for patients with metastatic renal cell carcinoma. Clin Genitourinary Cancer. 2009a; 7:28-33.

Motzer RJ, Hutson TE, Tomczak P*, et al.* Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009b; 27:3584-90.

Motzer, R.J., G.R. Hudes, M.S. Ginsberg*, et al.* Phase I/II trial of sunitinib plus gefitinib in patients with metastatic renal cell carcinoma. Am J Clin Oncol. 2010;33:614-618.

Motzer RJ, Michaelson MD, Redman BG*, et al.* Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 2006;24:16-24.

O'Farrell, A.M., T.J. Abrams, H.A. Yuen*, et al.* U11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. Blood 2003a; 101:3597-605

O'Farrell, A.-M., J.M. Foran, W. Fiedler, *et al*. An innovative phase I clinical study demonstrates inhibition of FLT3 phosphorylation by SU11248 in acute myeloid leukemia patients. Clin Cancer Res 2003b; 9:5465-5476.

Ogose A, Yazawa Y, Ueda T*, et al.* Alveolar soft part sarcoma in Japan: multi-institutional study of 57 patients from the Japanese Musculoskeletal Oncology Group. Oncology 2003;65:7-13.

Palassini E, Stacchiotti S, Negri T*, et al.* Sunitinib malate (SM) in alveolar soft part sarcoma (ASPS). J Clin Oncol ;28:A10014.

Patel, P.H., P.L. Senico, R.E. Curiel, R.J. Motzer, *et al.* Phase I study combining treatment with temsirolimus and sunitinib malate in patients with advanced renal cell carcinoma clinical genitourinary. Cancer 2009; 7: 24-27.

Pfeiffer P, Joergensen TL, Jensen BV*, et al.* Addition of bevacizumab or sunitinib to biweekly cetuximab and irinotecan as salvage therapy in patients with metastatic colorectal cancer after failure to CetIri. J Clin Oncol 2009;27: A15011.

Pfizer Inc. and Affiliates. Investigator's Brochure Sunitinib Malate. May 2009.

Porta C, Paglino C, Imarisio I, Bonomi L. Uncovering Pandora's vase: the growing problem of new toxicities from novel anticancer agents. The case of sorafenib and sunitinib. Clin Exp Med 2007;7: 127-34.

Portera CA, Jr., Ho V, Patel SR*, et al.* Alveolar soft part sarcoma: clinical course and patterns of metastasis in 70 patients treated at a single institution. Cancer 2001;91: 585-91.

Ramalingam SS, Mack PC, Vokes EE*, et al.* Cediranib (AZD2171) for the treatment of recurrent small cell lung cancer (SCLC): A California Consortium phase II study (NCI # 7097). J Clin Oncol 2008; 26:A8078.

Reichardt P, Lindner T, Pink D, Thuss-Patience PC, Kretzschmar A, Dorken B. Chemotherapy in alveolar soft part sarcomas. What do we know? Eur J Cancer 2003;39: 1511-6.

Rini BI, Tamaskar I, Shaheen P*, et al.* Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst 2007;99: 81-3.

Robert C, Soria JC, Spatz A*, et al.* Cutaneous side-effects of kinase inhibitors and blocking antibodies. Lancet Oncol 2005;6: 491-500.

Robinson, E.S., U.A. Matulonis, P. Ivy, et al. Rapid development of hypertension and proteinuria with cediranib, an oral vascular endothelial growth factor receptor inhibitor. *Clin J* Am Soc Nephrol 2010; 5(3): 477-83.

Rock EP, Goodman V, Jiang JX*, et al.* Food and Drug Administration drug approval summary: Sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma. Oncologist 2007;12: 107-13.

Roozendaal KJ, de Valk B, ten Velden JJ, van der Woude HJ, Kroon BB. Alveolar soft-part sarcoma responding to interferon alpha-2b. Br J Cancer 2003;89: 243-5.

Rosen L, Mulay M, Long J*, et al.* Phase I trial of SU011248, a novel tyrosine kinase inhibitor in advanced solid tumors. J Clin Oncol 2003;22:A765.

Rosenbaum SE, Wu S, Newman MA, West DP, Kuzel T, Lacouture ME. Dermatological reactions to the multitargeted tyrosine kinase inhibitor sunitinib. Support Care Cancer 2008;16: 557-66.

Royce, M., E.G. Chiorean, C. Sweeney, *et al*. A phase I dose-finding study of sunitinib in combination with capecitabine in patients with advanced solid tumors. ASCO Breast Cancer Symposium 2008; A169.

Rugo, H.S., J. Lyandres, M. Melisko, *et al.* Phase I study of sunitinib (SU) in combination with metronomic dosing of cyclophosphamide and methotrexate (CM) in patients with metastatic breast cancer (MBC). ASCO Breast Cancer Symposium 2008; A165.

Ryan CJ, Stadler WM, Roth B*, et al.* Phase I dose escalation and pharmacokinetic study of AZD2171, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinase, in patients with hormone refractory prostate cancer (HRPC). Invest New Drugs 2007; 25: 445-51.

Sakamoto KM. SU-11248 Sugen. Curr Opin Invest Drugs 2004; 5:1329-39.

Saltz LB, Rosen LS, Marshall JL*, et al.* Phase II trial of sunitinib in patients with metastatic colorectal cancer after failure of standard therapy. J Clin Oncol 2007;25:4793-9.

Schmidinger M, Zielinski CC, Vogl UM*, et al.* Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2008;26:5204-12.

Schmoll H, Cunningham D, Sobrero A, *et al*. mFOLFOX6 + cediranib vs mFOLFOX6 + bevacizumab in previously untreated metastatic colorectal cancer (mCRC): a randomized, double-blind, phase II/III study (HORIZON III). Ann Oncol 2010:21(Suppl 8):viii89, abstract 580O.

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1-10.

Smith TJ, Khatcheressian J, Lyman GH, *et al.* Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187-205.

Socinski MA, Novello S, Brahmer JR*, et al.* Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. J Clin Oncol 2008;26:650-6.

Sorensen AG, Batchelor TT, Zhang WT*, et al.* A "vascular normalization index" as potential mechanistic biomarker to predict survival after a single dose of cediranib in recurrent glioblastoma patients. Cancer Res 2009;69:5296-300.

Sridhar SS, Mackenzie MJ, Hotte SJ*, et al.* Activity of cediranib (AZD2171) in patients (pts) with previously untreated metastatic renal cell cancer (RCC). A phase II trial of the PMH Consortium. ASCO Meeting Abstracts 2008;26:5047.

Stacchiotti S, Tamborini E, Marrari A*, et al.* Response to Sunitinib Malate in Advanced Alveolar Soft Part Sarcoma. Clin Cancer Res 2009;15:1096-104.

Stadler WM. New targets, therapies, and toxicities: lessons to be learned. J Clin Oncol 2006;24: 4-5.

Starling N, Vazquez F, Cunningham D*, et al.* Phase I study to evaluate the safety and efficacy of sunitinib in combination with FOLFIRI in treatment-naive metastatic colorectal cancer (mCRC). J Clin Oncol 2008;26:A3563.

Stockwin LH, Vistica DT, Kenney S*, et al.* Gene expression profiling of alveolar soft-part sarcoma (ASPS). BMC Cancer 2009;9:22.

Suwattee P, Chow S, Berg BC, Warshaw EM. Sunitinib: a cause of bullous palmoplantar erythrodysesthesia, periungual erythema, and mucositis. Arch Dermatol 2008;144:123-5.

Sweeney, C., C. Verschraegen, G. Chiorean *et al.* A phase I dose escalation study of sunitinib plus capecitabine in patients with advanced solid tumors. J Clin Oncol 2007; 25:A3592.

Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. Ann Oncol 2008; 19: 1613-8.

Therasse, P., Arbuck, S.G., Eisenhauer E.A. *et al.* New Guidelines to Evaluate the Response to treatment in Solid Tumors. JNCI 2000; 92: 205-216

Traynor A.M., A.B. Sandler, J.H. Schiller, *et al*. Phase I dose-escalation and pharmacokinetic (PK) study of sunitinib (SU) plus docetaxel (D) in patients (pts) with advanced solid tumors (STs). J Clin Oncol 2008; 26:A3564

Vigil CE, Chiappori AA, Williams CA*, et al.* Phase II study of sunitinib malate (SM) in subjects with metastatic and/or surgically unresectable non-GIST soft tissue sarcomas. J Clin Oncol 2008; 26:A10535.

Wedge SR, Kendrew J, Hennequin LF*, et al.* AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. Cancer Res 2005; 65:4389-400.

Zhu AX, Sahani DV, di Tomaso E*, et al.* Sunitinib monotherapy in patients with advanced hepatocellular carcinoma (HCC): Insights from a multidisciplinary phase II study. J Clin Oncol 2008; 26:A4521.

Appendix A: Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix B: New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Appendix C: Potential Cytochrome P450 (CYP) Drug Interactions

Consult a frequently updated drug information reference regarding potential drug interactions.

Appendix D: Enzyme-Inducing Anticonvulsant Drugs

For drugs not listed, please contact the Study Chair.

Anticonvulsants with little or no enzyme induction	
Generic Name	*Trade Name*
Ethosuximide	Zarontin
Gabapentin	Neurontin
Lamotrigine	Lamictal
Levetiracetam	Keppra
Tigabine	Gabitril
Topiramate	Topamax
Valproic acid, divalproex	Depakote, Depakene
Zonisamide	Zonegran
Enzyme-inducing anticonvulsant drugs	
Generic Name	*Trade Name*
Carbamazepine	Tegretol
Felbamate	Felbatol
Phenobarbital	Phenobarbital
Phenytoin	Dilantin
Primidone	Mysoline
Oxcarbazepine	Trileptal

Appendix E: Medications That May Cause QTc Prolongation

The following table presents a list of drugs that prolong, may prolong, or are unlikely to prolong the QTc. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following Web site: *http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.*

Compound	Compound Half Life	Possible Washout Period – Hours	Possible Washout Period - Days
Alfuzocin	~10 hours		7
Amantadine	17 +/- 4 hours (10-25)		4
Amiodarone (cordarone)	58 days (15-142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hr (26-64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $T_{1/2}$=7-10 hour)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 +/- 7 hours		7
Cisapride	6 – 12 hour, up to 20 hour	60	
Clarithromycin	Non linear PK3-4 hr (250mg Q12) 5-7 hr (500mg Q12)	36	
Cloroquine	6 to 60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hr (4-10)	36	
Dofetilide	10 hr	48	
Dolesetron	8.1 hr		
Domperidone	7-8 hr	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	
Erythromycin	* Each salt form has different Half life*		
Felbamate	20-23 hr		5
Flecainide	20 hr (12-27)		5
Foscarnet	87.5+/-41.8 hours *distribution and release from bone*		20
Fosphenytoin	12-29 hr		6
Gatifloxacin	7-14 hr	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hr		3
Halofantrine	6-10 days (variable among individual)		45
Haloperidol	18 +/-5 hr		5
Ibutilide	6 hours (2-12) * variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isradipine	8 hours (multiple metabolites)	48	
Levofloxacin	6-8 hours	48	
Levomethadyl	Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20

Compound	Compound Half Life	Possible Washout Period – Hours	Possible Washout Period - Days
Lithium	24 hour (10-50)		7
Mesoridazine	24-48 hours (animal study)		10
Methadone	15-30 hours		7
Moexipril/HCTZ	2-9 hour (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	48	
Moxifloxacin	12 +/-1.3 hours	72	
Naratriptan	6 hours	36	
Nicardipine	~ 2 hour post IV infusion	12	
Nortriptyline*	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5 to 7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)		1 to 3
Pentamidine	6.4+/-1.3 hours	36	
Pimozide	55 hours		10
Procainamide	3-4 hour for PA and NAPA (active metabolite)	24	
Protiptyline*	> 24 hours, wide interpatient variability		
Quetiapine	6 hours	36	
Quinidine	6-8 hours in adult; 3-4 hours in children	36	
Quinine	4-5 hours		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T ½ =21-30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only one datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16-30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant		7
Tamoxifen	5-7 days (biphasic)		30
Telithromycin	2-3 hr	24	
Thioridazine	20-40 hours (Phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenifil	4 to 5 hours		
Venlaflaxine	5 +/-2 hours for parent comp. 11+-2 hours for OVD (active metabolite)	60	
Voriconizole	6 hours; dose dependent		
Ziprasidone	7 hr	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	18	

*Weakly associated with Torsades de Pointes and/or QT prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QT prolonging drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism).

References:

1. Physician's Desk Reference 2002
2. Facts and Comparisons (update to June 2005)
3. The Pharmacological Basis of Therapeutics 9th Edition, 1996

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Appendix F: Eligibility/Pre-Registration Worksheet

A Phase II Trial in Which Patients With Metastatic Alveolar Soft Part Sarcoma Are Randomized to Either Sunitinib or Cediranib Monotherapy, With Cross-Over at Disease Progression

Coordinating Center: NCI
Bethesda, MD 20892
Contact: Ashley Bruns
Phone: (240) 858-3162
Fax: (301) 451-5625
E-mail: ashley.bruns@nih.gov

Protocol Chair:
Alice Chen, MD
National Cancer Institute
Tel: (240) 781-3320
E-mail: chenali@mail.nih.gov

<table>
<tr><td colspan="2">Patient's Name: (FML)</td><td>Institution:</td></tr>
<tr><td colspan="2">Medical Record Number:</td><td>Investigator:</td></tr>
<tr><td colspan="2">Patient's Birth date:</td><td rowspan="2">Signature of Treating Physician</td></tr>
<tr><td colspan="2">Sex: _____male _____female</td></tr>
<tr><td colspan="2">IRB approval valid until (date):</td><td>Date Informed Consent was signed:</td></tr>
<tr><td>Race:
_____ Black
_____ Caucasian
_____ Asian
_____ American Indian
_____Native Hawaiian/ Pacific Islander
_____ Other
_____</td><td>Ethnicity:
___Hispanic
___Non-Hispanic
___Other:_____</td><td>Projected start date of treatment:</td></tr>
</table>

INCLUSION CRITERIA: All responses must be YES. A NO response will make the subject ineligible.

	Yes	No	N/A
Histologically documented (confirmed by the department of pathology at the institution where the patient is enrolled prior to patient enrollment) alveolar soft part sarcoma that is not curable by surgery. Block or 6 tumor sections available?			
Patients must show evidence of objective disease progression per RECIST 1 on scans within the 6 month period immediately preceding enrollment. Both scans used to determine disease progression should have been obtained within this 6-month period.			
Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See Section 11 for the evaluation of measurable disease.			
Any prior therapy must have been completed ≥4 weeks prior to enrollment on protocol and the participant must have recovered to eligibility levels from prior toxicity. Patients should be at least 6 weeks out from nitrosoureas and mitomycin C. Prior radiation should have been completed ≥4 weeks prior to study enrollment and all associated toxicities resolved to eligibility levels. Patients who have had prior monoclonal antibody therapy must have completed that therapy at least 3 half-lives of the antibody or 6 weeks ago. Patients who have received more than a cumulative dose of 350 mg/m^2 of doxorubicin may be enrolled at the discretion of the Coordinating Center PI after consultation with a cardiologist and if screening echocardiogram is normal. Patients must be ≥2 weeks since any investigational agent administered as part of a Phase 0 study (also referred to as an "early Phase I study" or "pre-Phase I study" where a sub-therapeutic dose of drug is administered) at the Coordinating Center PI's discretion, and should have recovered to eligibility levels from any toxicities.			
Patients with no prior therapy are eligible, provided they have metastatic disease that is not curable by surgery.			
Patients with newly diagnosed, unresectable, metastatic, and measurable ASPS who show clinical evidence of disease progression (including history and increasing physical symptoms) are eligible providing that on-study documentation includes a physician's rationale that supports evidence of clinical disease progression (i.e., increasing tumor pain).			
Age ≥ 16 years?			
If 16-17 years old, BSA ≥1.7 m^2 OR weight ≥60 kg?			
ECOG performance status ≤2 (please enter status _____), see Appendix A?			
Life expectancy of greater than 3 months?			

Patients must have normal organ and marrow function as defined below: a. Leukocytes >3,000/mcL b. Absolute neutrophil count >1,500/mcL c. Platelets >100,000/mcL d. Hemoglobin >9 g/dL e. Total serum bilirubin within normal institutional limits f. AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal g. Creatinine within normal institutional limits OR creatinine clearance >60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal	**Results:** WBC_____ Date_____ ANC_____ Date_____ Platelets_____ Date_____ Hgb_____ Date_____ Total Bilirubin_____ ULN_____ Date_____ AST(SGOT)_____ ULN_____ Date_____ ALT(SGPT)_____ ULN_____ Date_____ Creatinine_____ ULN_____ Date_____ **OR** Creatinine clearance_____ Date_____			
QTc <480 msec (with Bazett's correction)?	EKG Date_____ QTc_____			
The following groups of patients are eligible after consultation with a cardiologist and at the Coordinating Center PI's discretion, provided they have New York Heart Association Class II (NYHA; see Appendix B) cardiac function on baseline ECHO: o those with a history of Class II heart failure who are asymptomatic on treatment o those with prior anthracycline exposure greater than a cumulative dose of 350 mg/m^2 o those who have received central thoracic radiation that included the heart in the radiotherapy port.				
BP ≤ 140 mmHg (systolic) and ≤ 90 mmHg (diastolic). Initiation or adjustment of BP medication is permitted prior to study entry provided that the BP reading prior to enrollment is ≤ 140/90 mmHg.	BP reading_____ Date_____			
Patients who require potent CYP3A4 inducers or inhibitors and cannot switch medications must have their case reviewed by the Coordinating Center PI and may be enrolled only after discussion with and agreement from the Coordinating Center PI. Eligibility of patients receiving any medications or substances known to affect or with the potential to affect the activity or PK of cediranib will be determined following review of their case by the Coordinating Center PI.				
Agree to use two reliable forms of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 2 months following study drug discontinuation.				

Has a signed informed consent/assent been obtained by the patient or parent/legal guardian?				
Left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal?	ECHO Date_____ LVEF_____			
Able to swallow whole tablets and capsules?				

EXCLUSION CRITERIA: Responses should be NO

		Yes	**No**	**N/A**
Uncontrolled intercurrent illness including, but not limited to hypertension, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.				
Major surgery within 4 weeks prior to entry into the study, or a surgical incision that is not fully healed.				
Any of the following conditions: serious or non-healing wound, ulcer; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment; coronary/peripheral artery bypass graft or stenting within the past 12 months; or cerebrovascular accident (CVA) or transient ischemic attack within the past 12 months.				
Any condition (e.g., gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, or active peptic ulcer disease) that impairs the patient's ability to swallow, retain, and/or absorb the drug?				
Taken potent inhibitors or inducers of CYP3A4 in the past 7 or 12 days, respectively? (Eligibility will be determined following a review of their case by the Coordinating Center PI.)				
History of familial long QT syndrome, or use of medications that may cause QTc interval prolongation (Appendix E)?				
Pre-existing thyroid abnormality and unable to maintain thyroid function in the normal range with medication?				
Greater than 2+ proteinuria on two consecutive dipsticks taken no less than 1 week apart or 24-hour urine protein of > 1 g? (Patients with < 2+ proteinuria are eligible following initial determination by urinalysis within 1 week prior to enrollment and do not need the urinalysis repeated.)				
Receiving any other investigational agents?				
Prior treatment with any VEGF receptor tyrosine kinase inhibitor (e.g., cediranib, sunitinib, pazopanib, sorafenib)? (Prior treatment with bevacizumab is allowed.)				
Pregnant?	Pregnancy Test Date:			
Breastfeeding?				
HIV-positive on combination antiretroviral therapy?				
Requires use of warfarin or its derivatives? (Note: Low molecular weight heparin is permitted if clinically indicated.)				

Pre Study Eligibility Screening Evaluations (required within the designated number of days prior to patient enrollment):	**Date Done:**
History and Physical Exam (8 days)	
Height, Weight, vital signs, EKG, and performance status (8 days)	
CBC, Diff, Plts, Blood Chemistries* (8 days) * Na^+, K^+, phosphorus, magnesium, Creatinine, BUN, calcium, glucose, albumin, SGPT (ALT), SGOT (AST), Alkaline Phos, Bilirubin, total protein, TSH	
Troponin T or I (8 days)	
Urinalysis (8 days)	
Appropriate anatomic imaging studies (28 days)	
EKG (8 days)	
Echo (28 days)	
Pregnancy Test (8 days if clinically indicated)	

DESCRIPTIVE FACTORS:

Primary: _____ Histology: _____

Other Chronic Diseases: Y / N (If yes, please explain):

PRIOR THERAPY (Please specify date, procedure, agent, dose, response)

YES	NO	
____	____	1. **Surgery/Biopsy:**
____	____	2. **Chemotherapy:**
____	____	3. **Radiotherapy**:
____	____	4. **Hormonal Therapy:**
____	____	5. **Immunotherapy**:

Physician's Signature: _____ Date: _____

Printed Name of Physician: _____

To be completed by participating center when registering a patient:

Date Registered with NCI _____/_____/_____
Spoke With: _____
Study ID: _____
Eligibility Checklist Completed By: _____
Assigned CRA / Data Manager: _____

A confirmation of registration will be sent to you by the NCI.

Participant Status Updates Form

Complete form and send via encrypted email to NCI Central Registration Office (HOIS) at ncicentralregistration-l@mail.nih.gov **AND fax or email to the Coordinating Center Research Nurse at** (240) 858-3162 ashley.bruns@nih.gov

Patient Information:

First name _____ *Last name* _____ *Middle initial* _____

*ID number:*_____

*Protocol Number (CC# preferred):*_____

Off Treatment Date (mm/dd/yy):_____

Off Treatment Reason:_____

Off Study Date (mm/dd/yy): _____

Choose one of the following off-study reasons:

_____ *C: Completed Study*
_____ *L: Lost to follow-up*
_____ *R: Refused Further Treatment*
_____ *T: Toxicity*
_____ *D: Death*
_____ *P: Progressive Disease*
_____ *O: Other*

Death Date: (mm/dd/yy): _____

Choose one or more of the following DOD Sources:

*Social Security Death Index SS#:*_____ *http://ssdi.rootsweb.com/*

Obituaries
*Document:*_____*http://www.legacy.com/washingtonpost/DeathNotices*

Cause of
*Death:*_____

Place of
*Death:*_____

*Family/staff member name notifying DOD:*_____

Registrar:

*Name:*_____

*Work Phone:*_____ *Today's Date***:** _____

Comments:

Appendix G: Study Diary
Page 1 Cediranib

CTEP-assigned Protocol # _____

Local Protocol # _____

Cycle Number _____

Today's date _____

Patient Name_____ Patient Study ID _____
(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of cediranib each day at approximately the same time. Please take the tablet(s) on an empty stomach at least 1 hour before or 2 hours after meals. You will take ____15 mg tablets and ____ 20 mg tablets every morning.
3. Record the date, the number of tablets of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	Day	Time of daily dose	# of tablets taken		Blood Pressure	Comments
			15 mg	20 mg		
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	13					
	14					

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

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

Physician/Nurse/Data Manager's Signature _____

Appendix G: Study Diary
Page 2 Cediranib

CTEP-assigned Protocol # _____

Local Protocol # _____

Cycle Number _____

Today's date _____

Patient Name_____ Patient Study ID_____
(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of cediranib each day at approximately the same time. Please take the tablet(s) on an empty stomach at least 1 hour before or 2 hours after meals. You will take ____15 mg tablets and ____ 20 mg tablets every morning.
3. Record the date, the number of tablets of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	Day	Time of daily dose	# of tablets taken		Blood Pressure	Comments
			15 mg	20 mg		
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

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

Physician/Nurse/Data Manager's Signature _____

Appendix G: Study Diary
Page 1 Sunitinib

CTEP-assigned Protocol # _____

Local Protocol # _____

Cycle Number _____

Today's date _____

Patient Name_____ Patient Study ID_____
(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of **sunitinib** each day in the morning. You will take ___12.5 mg capsules and ___ 25 mg capsules every morning. You may take the capsules with or without food as you wish.
3. Record the date, the number of capsules of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	Day	Time of daily dose	# of capsules taken		Blood Pressure	Comments
			12.5 mg	25 mg		
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	13					
	14					

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

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

Physician/Nurse/Data Manager's Signature _____

Appendix G: Study Diary
Page 2 Sunitinib

CTEP-assigned Protocol # _____

Local Protocol # _____

Cycle Number _____

Today's date _____

Patient Name_____ Patient Study ID_____
(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of **sunitinib** each day in the morning. You will take ____12.5 mg capsules and ___ 25 mg capsules every morning. You may take the capsules with or without food as you wish.
3. Record the date, the number of capsules of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	Day	Time of daily dose	# of capsules taken		Blood Pressure	Comments
			12.5 mg	25 mg		
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

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

Physician/Nurse/Data Manager's Signature _____

Appendix G: Study Diary
Page 1 Sunitinib DL -2 Only

CTEP-assigned Protocol # _____

Local Protocol # _____

Cycle Number _____

Today's date _____

Patient Name_____ Patient Study ID_____
(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of **sunitinib** each day in the morning for 3 weeks (Days 1-21). You will take ____12.5 mg capsules and ____ 25 mg capsules. You may take the capsules with or without food as you wish.
   During week 4 (Days 22-28), you will not take sunitinib.
3. Record the date, the number of capsules of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	Day	Time of daily dose	# of capsules taken		Blood Pressure	Comments
			12.5 mg	25 mg		
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	13					
	14					

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

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

Physician/Nurse/Data Manager's Signature _____

Appendix G: Study Diary
Page 2 Sunitinib DL -2 Only

CTEP-assigned Protocol # _____

Local Protocol # _____

Cycle Number _____

Today's date _____

Patient Name_____ Patient Study ID_____
(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of **sunitinib** each day in the morning for 3 weeks (Days 1-21). You will take ____12.5 mg capsules and ____ 25 mg capsules. You may take the capsules with or without food as you wish.
   During week 4 (Days 22-28), you will not take sunitinib.
3. Record the date, the number of capsules of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	Day	Time of daily dose	# of capsules taken		Blood Pressure	Comments
			12.5 mg	25 mg		
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	~~22~~	~~NO DRUG~~				
	~~23~~	~~NO DRUG~~				
	~~24~~	~~NO DRUG~~				
	~~25~~	~~NO DRUG~~				
	~~26~~	~~NO DRUG~~				
	~~27~~	~~NO DRUG~~				
	~~28~~	~~NO DRUG~~				

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

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

Physician/Nurse/Data Manager's Signature _____

Appendix H: Blood Pressure Collection and Recording

General Guidelines
Frequency of monitoring: Blood pressure will be monitored every 2 weeks by any health care provider during the first cycle of Part I and Part II, then at the start of every cycle for the duration of treatment (unless patients have experienced elevated blood pressure requiring drug therapy, at which point the frequency of BP monitoring by a health care provider will be determined by the local PI). Patients on study for 2 years or longer will have their blood pressure monitored at the start of every third cycle. Additionally, all patients will be required to monitor their BP at home at least once a day while on study and record the readings in the Study Diary (Appendix G).

Data recording: All required data should be recorded in the appropriate eCRF or on the patient's blood pressure monitoring diary, as appropriate. **The following data are required at baseline and at each subsequent assessment**:

- Assessment date and time
- Pulse
- Systolic and diastolic BP

Risk factors for hypertension (assess and record data in eCRF)

- Diabetes (type 1 or type 2)
- Renal disease (specify on CRF)
- Endocrine condition associated with HTN (specify on CRF)
- Use of steroids or NSAIDs (specify all concomitant meds)
- Underlying cardiovascular condition – specify (i.e., ischemic heart disease)

Baseline data collection (at registration)
All patients**:**

- Current BP
- Proteinuria, if present

Patients with preexisting hypertension (i.e., those for whom "hypertension" is entered as a concomitant condition at registration, or those who are currently receiving therapy with antihypertensive medication) – also record:

- Date of HTN diagnosis (original)
- Type HTN (essential or secondary)
- CTCAE v5.0 grade of HTN (at time of study entry)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of the following:
    - Antihypertensive agents taken at study entry
    - Antihypertensive agents taken in past (e.g., discontinued for toxicity, lack of efficacy)

Follow up BP data collection (while on study)
All patients (at each clinic visit):

- Current BP
- Proteinuria, if present

Patients with treatment-emergent hypertension [defined as >140/90] – record at time of hypertension diagnosis and at all subsequent visits:

- BP changes from baseline (or from previous assessment) (specify grade changes per Table in Appendix I)
- Hypertension-related symptoms as reported by patient (e.g., headache)
- Other relevant changes associated with development of hypertension (e.g., ECG abnormalities)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of currently prescribed antihypertensive agents

Patients with preexisting hypertension at study entry – record at each visit:

- BP changes from previous clinic visit (specify grade changes per Table in Appendix I)
- Hypertension-related symptoms reported by patient (e.g., headache)
- Other relevant changes associated with development of hypertension (e.g., ECG abnormalities)
- Changes in antihypertensive medications since last assessment (e.g., dose change, add/discontinue drug)

*Classes of antihypertensive drugs include ACE inhibitors, calcium channel blockers, alpha blockers, beta blockers, diuretics, angiotensin II receptor antagonists.

Appendix I: Management of Hypertension

Recommended Hypertension Monitoring and Management

(BP in mmHg)

Grade (CTCAE v5)	Antihypertensive Therapy	Blood Pressure Monitoring	Sunitinib/Cediranib Dose Modification
Persistent Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-89		Standard	No change
Persistent Grade 2-Moderate Systolic 140-159 Diastolic 90-99 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v5	Step 1) Initiate LA DHP CCB treatment and if needed, after 24-48 hr Rx, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at max dose of Rx Step 2) If BP still not controlled, add another antihypertensive Rx, a BB, ACE1, ARB, or ABB; increase dose of this drug as described in step 1 Step 3) If BP still not controlled, add 3rd drug from the list of antihypertensives in step 2; increase dose of this drug as described in step 1 Step 4) If BP still not controlled, consider either 1 dose reduction of sunitinib/cediranib or stopping sunitinib/cediranib *NOTE: Stopping or reducing the dose of sunitinib/cediranib is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly.*	BP should be monitored as recommended by the treating physician	No change except as described in step 4

Persistent Grade 3 Severe Systolic ≥160 Diastolic ≥100 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v5	HOLD sunitinib/cediranib until systolic BP ≤159 and diastolic BP ≤99. BP management is identical to that for Grade 2 (see steps 1-4 above) **with 2 major exceptions:** **1) If systolic BP >180 or diastolic BP >110 and the patient is symptomatic: optimal management with intensive IV support in ICU; STOP sunitinib/cediranib and notify hospital staff that stopping sunitinib/cediranib may result in a decrease in BP** **and** **2) If systolic BP >180 or diastolic BP >110 and the patient is asymptomatic, 2 new anti-hypertensives must be given together in step 1 (and dose escalated appropriately as in step 1).** *NOTE: Stopping or reducing the dose of sunitinib/cediranib is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*	BP should be monitored as recommended by the treating physician **unless the patient is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive.**	HOLD sunitinib/cediranib until systolic BP ≤159 and diastolic BP ≤99. In most circumstances, if BP cannot be controlled after an optimal trial of anti-hypertensive medications, consider either 1 dose reduction of sunitinib/cediranib or stopping sunitinib/cediranib. **HOWEVER, if the patient requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110,** permanently discontinue sunitinib/cediranib or if BP is controlled, re-start sunitinib/cediranib at 1 lower dose level after consultation with the study Principal Investigator
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; STOP sunitinib/cediranib and notify hospital staff that stopping sunitinib/cediranib may result in a decrease in BP**	Intensive	Permanently discontinue sunitinib/cediranib or if BP is controlled, re-start sunitinib/cediranib at 1 lower dose level after consultation with the study Principal Investigator

Abbreviations: dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), alpha beta blocker (ABB)

- If patients require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
- If patients require >2 dose reductions, discontinue protocol therapy
- Patients may have up to 2 drugs for management of hypertension prior to any dose reduction in sunitinib/cediranib
- 24-48 hours should elapse between modifications of anti-hypertensive therapy
- Hypertension should be graded using CTCAE v5.

Oral Antihypertensive Medication List

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

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetolol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

Appendix J: LVEF Dose Modification Table

Asymptomatic Decrease in LVEF

The decision to continue or hold STUDY DRUG is based on the LVEF as it relates to the institutions'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 ECHO within 1-2 cycles
1-5% below LLN	Continue and repeat ECHO within 1-2 cycles	Continue and repeat ECHO within 1-2 cycles	HOLD and repeat ECHO within 1-2 cycles
≥ 6% below LLN	Continue and repeat ECHO within 1-2 cycles	HOLD and repeat ECHO within 1-2 cycles	HOLD and repeat ECHO within 1-2 cycles

Discontinue STUDY DRUG if:

- Two consecutive HOLD catagories occur.

- Three intermittant HOLD catagories occur (at the discretion of the investigator, STUDY DRUG may also be permanently discontinued prior to the occurance of 3 intermittant HOLD catagories).

If LVEF is maintained at a "Continue and repeat ECHO" or improves from a HOLD to a "Continue and repeat ECHO" category, additonal echocardiograms prior to the next scheduled ECHO will be at the discretion of the investigator.

Symptomatic Cardiac Events

Discontinue STUDY DRUG if:

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

Appendix K: CTEP Multicenter Guidelines

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

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

Appendix L: Information on Possible Interactions with Other Agents for Patients and their Caregivers and Non-study Health Care Team

Sunitinib

The patient _____ is enrolled on a clinical trial using the experimental agent sunitinib. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

Sunitinib interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the counter remedy), or anything that you buy from the health food store or grocery store (herbal supplement).

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants, or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you**. These are the things that you and they need to know:

- Sunitinib is metabolized (converted in the body) by a liver enzyme called CYP3A4. Sunitinib must be used very carefully with other medicines that need this liver enzyme to be effective or to be cleared from your system.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of CYP3A4."
- Your regular prescribers should look at a frequently updated drug information reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and printed on the ingredient list. Find the generic name (your pharmacist can help) and look at the table on the back of this page. Be careful.
- You should not take St. John's wort or grapefruit juice with sunitinib.
- You should not receive steroids unless they are absolutely necessary; tell your study doctor if you are taking, have a prescription for, or have been given steroids.
- You should not take drugs that affect your heart rhythm. Tell your study doctor if you are taking, have a prescription for, or have been given such heart medications.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at _____.

Cediranib

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

These are the things that you as a prescriber need to know:
Cediranib (AZD2171) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

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

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

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

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

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

  medicine. Your study doctor's name is _____

  and he or she can be contacted at _____.

June 2016

STUDY DRUG INFORMATION WALLET CARD

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

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

  and can be contacted at _____.

Appendix M: Informed Consent Form Template for Cancer Treatment Trials

Study Title: A Phase II Trial in Which Patients With Metastatic Alveolar Soft Part Sarcoma Are Randomized to Either Sunitinib or Cediranib Monotherapy, With Cross-Over at Disease Progression

Introduction

We invite you to take part in this research study.

First, we want you to know that:

Taking part in this research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with family, friends or your personal physician or other health professional.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, the drugs cediranib and sunitinib have on you and your alveolar soft part sarcoma. This study will also help to find out how cediranib and sunitinib work in patients who have your type of cancer. The 2 drugs will not be given in combination during this study. You will receive one drug (either cediranib or sunitinib) until that drug is no longer working to control your cancer or you have too many side effects, and then the other drug will be given.

Cediranib is an experimental drug not yet approved by the Food and Drug Administration. Sunitinib has been approved for treating a certain type of kidney cancer and gastrointestinal cancer, but is considered experimental in the treatment of alveolar soft part sarcoma. Cediranib and sunitinib work by blocking the creation of new blood vessels. All solid tumors need new blood vessels to grow. We hope cediranib and sunitinib will stop tumor growth by preventing the growth of new blood vessels. So far, more than 800 patients have taken part in clinical trials

of cediranib, including more than 40 patients with alveolar soft part sarcoma. More than 8,000 patients have received sunitinib, and at least 10 of these patients had alveolar soft part sarcoma. Some patients with alveolar soft part sarcoma treated with cediranib or sunitinib had tumors that either decreased in size or remained stable without growth for a prolonged period of time. Both cediranib and sunitinib are considered experimental drugs for your type of cancer.

How many people will take part in the study?
Up to 70 patients with alveolar soft part sarcoma will take part in this study across several centers in the United States.

Description of Research Study
What will happen if you take part in this research study?
After you are accepted for this study and you choose to take part, you will be "randomized" into one of the treatment groups (called "arms"). Randomization means that you are put into a group by chance. A computer program will place you in one of the treatment arms. Neither you nor your doctor can choose the treatment arm you will be in. This study is divided into two parts. During Part I, you will begin taking cediranib or sunitinib (depending on which arm you are in) by mouth once a day, every day. The treatment will be given in cycles. Each cycle is 28 days long. You will continue taking the study drug assigned to you (either cediranib or sunitinib) until that drug is no longer working to control your cancer, or you have too many side effects. After this happens, you will not get a study drug for 2 weeks before beginning Part II of the study. During Part II, you will receive the other study drug (either cediranib or sunitinib) that you did not take during Part I. However, if too many patients in a treatment arm have serious side effects or not enough patients have disease that responds, that treatment arm may be closed to new patients. If the other treatment arm is closed, you would not receive the other drug and your participation in the study would end after you complete Part I. Currently, the cediranib treatment arm for patients with newly diagnosed ASPS is closed. No patients will enroll or cross over to this arm to receive cediranib.

Cediranib and sunitinib can be taken while you are an outpatient. You will take either cediranib or sunitinib during Part I and switch to the other drug during Part II. You are to swallow the tablets or capsules whole at about the same time each morning. Cediranib must be taken on an empty stomach, 1 hour before or 2 hours after meals. Sunitinib can be taken with or without food as you wish. You should write down the number of pills you take and the time you took them in the diary that your study team will give you. If you miss doses, please write this in your diary. If you remember your missed dose within 3 hours of the time you usually take a dose, you can take enough pills to make up for the missed dose; if not, do not make up the missed dose. The dose will be changed if you have any serious side effects. This will be determined by your study team.

Standard procedures being done because you are in this study; these may be done more often because you are in the study:

- **Clinic visit** to ask how you are feeling and to evaluate you with a physical examination at the start of each cycle (every 4 weeks) (every 3 cycles for patients on study for 2 years or longer)

- **Vital signs:** You will need to have your vital signs (measurement of your temperature, breathing rate, and blood pressure) measured each time you are seen in the outpatient clinic. You will also need to have your blood pressure measured by a health care provider every 2 weeks for the first cycle of Part I and Part II. If you have high blood pressure and need medication to control it, the study doctor will tell you how often you will need to have your blood pressure checked during the study. We will also ask you to measure your own blood pressure at home each day for the entire study. If your blood pressure is ever more than 150/90, or if the diastolic pressure (the bottom number) increases by more than 20, you should call the research team. You should also call the research team if you experience any symptoms of high blood pressure, such as chest pain, shortness of breath, headache, blood in the urine, or double vision.
- **Blood tests:** Measurement of your white blood cells, red blood cells and platelets, and measurements of your blood sugar and electrolytes and of how your liver and kidneys work, will be done every 2 weeks for the first 2 cycles of Part I and Part II and then at the start of all other cycles (every 3 cycles for patients on study for 2 years or longer). Doing all of these blood tests will require 1-2 tablespoons (20-30 mL) of blood each time.
- **Urine test:** You will be asked to give a urine sample for testing at the start of each cycle, (every 3 cycles for patients on study for 2 years or longer) or more often if your results have been abnormal. Depending on the results, you may be asked to collect your urine for 24 hours for further testing.
- **Pregnancy test** in women who are able to become pregnant before you start cediranib or sunitinib and before you start Part II.
- **EKGs** (a recording of the heart's electrical activity) to check your heart will be done before you start cediranib or sunitinib, before you start Part II, and at the start of each cycle (every 3 cycles for patients on study for 2 years or longer) to check for signs of possible damage to your heart.
- **Echocardiogram** to check your heart will be done before you start cediranib or sunitinib, before you start Part II, and at other times if needed to check for signs of possible damage to your heart. If abnormal, a repeat echocardiogram will be done every 2 cycles.
- **CT scans (a computerized x-ray examination)** or other imaging tests such as ultrasound (an examination using sound waves) or MRI (an examination using magnetic field and radio waves) that detect your tumor will be done every 2 cycles. PET scans (a scan that detects a small amount of radioactive substance that has been injected through a vein) will also be done at the start of the study and may be repeated. This is done so that any benefit of the drug can be seen, and so that if your cancer is not responding to the drug, the study team can tell you and help you move to a different treatment program (discussed further below).
- Plain x-ray: If you are younger than 18 years old, an x-ray of your lower legs will be taken to see if your bones have stopped growing before you start cediranib or sunitinib. This test is done because in some growing animals that received drugs similar to cediranib or sunitinib, changes in the structure of the bones were seen. The x-ray will only be repeated if your study doctor thinks it is necessary.

Tests and procedures that are either being tested in this study or being done to see how the drug is affecting your body:

- Measurement of cediranib in your blood: We will collect multiple blood samples throughout the study to measure the amount of cediranib in your blood and to help us find out how the body handles cediranib. Please see the study chart for more details. The total blood for all these tests will be about 1~2 tablespoons.

When you are finished taking study drugs
You can take part in this study until either you or your study team decides that the study drugs are not helping you. If the first drug you are taking (either cediranib or sunitinib) is not helping you, you can move on to Part II of the study and receive the other drug if that treatment arm is open to new patients. Your taking part is voluntary, so you can stop taking cediranib or sunitinib at any time, but we ask that you speak to your study team before stopping the study drug.

Your study team will be watching you and your cancer during the study. If your cancer is clearly getting worse during Part II of the study, then your study team will stop the study treatment. At the end of the study, we will check with you or your local doctor for 30 days after you stop taking cediranib or sunitinib to see how you are doing. No more testing will be required.

Study Chart
The treatment is given over 28-day periods of time called cycles. The 28-day treatment cycle will be repeated as long as you are not having serious side effects and your cancer is either steady or getting better. If the drug you receive during Part I of the study is no longer working to control your cancer or you have too many side effects, you can move on to Part II of the study and get the other drug if that treatment arm is open. Before you start Part II of the study there will be 2 weeks during which you get no study drug. This is called a "wash-out" period. You will also need to have certain tests repeated to make sure it is safe for you to start Part II of the study.

Each cycle is numbered. The chart below shows what will happen to you during Cycle 1 and future cycles. The left-hand column shows the day in the cycle and the right-hand column tells you what will happen on that day. This schedule lists what will happen to you after you sign the consent form and start the study. The cycle numbers will start at 1 again when you begin Part II of the study.

Cycle 1 (Part I and Part II)

Day	What to do and what will happen to you
Before starting study treatment	• Get routine blood and urine tests • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider (HCP) • Imaging tests will be done • EKG and echocardiogram will be done to check your heart • Pregnancy test

Cycle 1 and Future cycles (Part I and Part II)

Day	What to do and what will happen to you
Days 1-28	• Have a history taken of how you feel and undergo a physical examination by a Health Care Provider (HCP) at the start of each cycle • Get routine blood tests every 2 weeks for the first 2 cycles, then at the start of each cycle (every 3 cycles for patients on study for 2 years or longer). • Urine sample for routine tests at the start of each cycle • Have your blood pressure checked by a health care provider every 2 weeks during cycle 1, then at the start of each cycle (every 3 cycles for patients on study for 2 years or longer) • Take cediranib or sunitinib, as given, once a day if you have no bad side effects and your cancer is not getting worse. Call the research nurse or your study doctor if you do not know what to do. • Measure your blood pressure at home every day • Imaging tests will be done every 2 cycles to find out how your tumor is responding (every 3 cycles for patients on study for 2 years or longer) • EKGs and echocardiograms will be done to check your heart • Blood samples to measure cediranib will be taken at the following time points before taking the drug: before your first dose, on cycle 1 day 15, on cycle 2 day 1, on cycle 3 day 1, and on cycle 4 day 1.

Stopping Therapy
Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment (if this happens during Part I, you may still go on to Part II of the study, as long as the other treatment arm has not been closed)
- if you have side effects from the treatment that your doctor thinks are too severe (if this happens during Part I, you may still go on to Part II of the study, as long as the other treatment arm has not been closed)
- if new information shows that another treatment would be better for you

In this case, you will be told the reason why cediranib or sunitinib is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI) or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained

for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases **cannot** be recalled and destroyed.

Alternative Approaches or Treatments
What other choices do I have if I do not take part in this study?
Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Risk or Discomforts of Participation
What side effects or risks can you expect from being in the study?
If you choose to take part in this study, there is a risk that the study drug(s) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The study drug(s) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.

- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

- One patient on this study experienced bleeding in his brain around his cancer. The study drug may have contributed to the bleeding risk. This condition can keep oxygen from reaching the brain and cause brain damage or death.

Studies have shown high blood pressure to be one common side effect of cediranib and sunitinib. Your blood pressure will be closely watched while you are taking cediranib or sunitinib. This will include having your blood pressure measured every 2 weeks by a health care provider for the first cycle and you checking your blood pressure at home once a day for the entire study. If you have high blood pressure while taking cediranib or sunitinib, your study doctor may recommend follow-up with your primary care physician and/or starting or increasing medication to lower blood pressure.

We do not know if cediranib and sunitinib will have any effect on the bone growth of patients who have not finished growing. Please talk to your doctor or the research team about how this might affect the growth of a young patient.

Grapefruit juice has been shown to affect how the body handles some drugs by blocking the activity of the body's cytochrome P450 (CYP450) system. CYP450 is important in breaking down substances in the body, including sunitinib and many other drugs. Therefore, please avoid grapefruit juice while taking cediranib or sunitinib. The herbal supplement St. John's wort can also affect blood levels of drugs such as sunitinib, and should be avoided. We do not know if taking cediranib or sunitinib will cause other drugs you may be taking to work differently. **It is very important that you talk to a member of the research team before beginning any new drugs, over-the-counter medications, vitamins, or alternative therapies.**

Risks and side effects related to cediranib include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving cediranib (AZD2171), more than 20 and up to 100 may have:
• Diarrhea, nausea • Tiredness • Loss of appetite • Changes in voice • High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cediranib (AZD2171), from 4 to 20 may have:

- Pain
- Constipation, vomiting
- Dry mouth
- Difficulty swallowing
- Sores in the mouth
- Infection
- Bruising, bleeding
- Weight loss
- Dehydration
- Muscle weakness
- Dizziness, headache
- Cough, shortness of breath, sore throat
- Redness, pain or peeling of palms and soles
- Blood clot which may cause swelling, pain, shortness of breath, confusion, or paralysis

RARE, AND SERIOUS
In 100 people receiving cediranib (AZD2171), 3 or fewer may have:

- Anemia, kidney problems which may cause tiredness, bruising, swelling, or may require dialysis
- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- A tear or hole in internal organs that may require surgery
- Liver damage which may cause yellowing of eyes and skin, swelling
- Non-healing surgical site
- Damage to the brain which may cause changes in thinking
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Kidney damage which may require dialysis
- Blood clot in artery which may cause swelling, pain, shortness of breath or change of color in extremity

Risks and side effects related to sunitinib include:

COMMON, SOME MAY BE SERIOUS
In 100 people receiving sunitinib malate (SU011248 L-malate), more than 20 and up to 100 may have:

- Pain
- Constipation, diarrhea, heartburn, nausea, vomiting
- Sores in the mouth
- Tiredness
- Loss of appetite
- Changes in taste
- Sore throat
- Redness, pain or peeling of palms and soles

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving sunitinib malate (SU011248 L-malate), from 4 to 20 may have:
• Anemia which may require blood transfusion • Blurred vision with chance of blindness • Bloating, passing gas • Dry mouth, skin • Chills, fever • Swelling of arms, legs • Flu-like symptoms including body aches • Bruising, bleeding • Weight loss • Infection, especially when white blood cell count is low • Dehydration • Dizziness, headache • Feeling of "pins and needles" in arms and legs • Depression • Difficulty sleeping • Cough, shortness of breath • Nose bleed • Hair loss, rash, itching, skin changes • Change in hair color • High blood pressure which may cause headaches, dizziness, blurred vision

RARE, AND SERIOUS In 100 people receiving sunitinib malate (SU011248 L-malate), 3 or fewer may have:
• Anemia, kidney problems which may cause tiredness, bruising, swelling, or may require dialysis • Blood clot which may cause confusion, paralysis, seizures or swelling, pain, shortness of breath • Damage to organs (heart, brain, others) which may cause shortness of breath, swelling of ankles, and tiredness, changes in thinking • Heart failure, heart attack which may cause shortness of breath, swelling of ankles, and tiredness • Pain and swelling of thyroid • Visual loss • Difficulty swallowing • A tear or hole in or between internal organs which may cause drainage and may require surgery • Swelling of the gallbladder • Liver damage which may cause yellowing of eyes and skin, swelling • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Flesh-eating bacteria syndrome

- Non-healing surgical site
- Change in the heart rhythm
- Kidney damage which may require dialysis
- Damage to the jawbone which may cause loss of teeth
- Damage to muscle which may cause muscle pain, dark red urine
- Cancer of bone marrow caused by chemotherapy
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- Stroke
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Sores on the skin
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Reproductive Risks: If you are a woman who is breast feeding or pregnant, you may not take part in the study because we do not know how cediranib or sunitinib would affect your baby or your unborn child. You should not become pregnant or father a baby while on this study and for 2 months after you stop taking the drug because the drugs in this study can affect an unborn baby. It is important you understand that you and your partner need to use **2** forms of effective birth control (examples below) while on this study and for 2 months after the study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.
Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

For more information about risks and side effects, please ask your study team.

Potential Benefits of Participation
Are there benefits to taking part in the study?
The aim of this study is to see if either cediranib or sunitinib will cause your tumors to shrink. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drugs' effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Research Subject's Rights

What are the costs of taking part in this study?
You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The study agents, cediranib and sunitinib, will be provided free of charge while you are participating in this study. Even though it is unlikely, there is a possibility that at some point the supply of study agent may run out necessitating taking you off-study. If this would occur, other possible options are:

- You might be able to get the cediranib or sunitinib from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.

- If there is no cediranib or sunitinib available at all, no one will be able to get more and the study would close.

If a problem with getting cediranib or sunitinib occurs, your study doctor will talk to you about these options.

[If applicable, inform the patient of any tests, procedures or agents for which there is no charge. The explanation, when applicable, should clearly state that there are charges resulting from performance of the test or drug administration that will be billed to the patient and/or health plan. For example, "The NCI is supplying (drug) at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the (drug)."]

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if you are injured because you took part in this study?
It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are your rights if you take part in this study?
Taking part in this study is your choice. You may choose either to take part or to not take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. You can still get your medical care from our institution if you are eligible and choose to participate in another trial.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Will your medical information be kept private?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Institutional Review Board
- Qualified representatives from the pharmaceutical collaborators providing cediranib and sunitinib may also review the medical records.
- Designees from other cancer centers participating in this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information will be used for auditing or program evaluation internally by the NIH; or

- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237). You may also visit the NCI Web site at http://cancer.gov/.

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Appendix N: Shipping Manifest to NCI

Ship From: Address: Phone: Contact Name: Clinical Site:	**Shipping Manifest**	**Ship To:** **Attn: Ashley Bruns, RN** Developmental Therapeutics Clinic National Cancer Institute Bldg 10 RM 8D53 Bethesda, MD 20892 **Telephone**: (240) 858-3162 **Fax**: (301) 451-5625 **E-mail:** ashley.bruns@nih.gov

Shipping Date: **Carrier:**

Clinical Protocol: CTEP #8875

In Package	Unique Patient ID*	Description	Number of items	Comments
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*Use 4-digit CTSU numbers. **Do NOT include patient identifiers.**

Appendix O: PK Evaluation of Cediranib

Pharmacokinetic analysis will be performed only on samples from patients on cediranib (both as upfront therapy and following cross-over). No PK sampling and analysis will be done for patients receiving sunitinib.

Blood samples for PK analyses will be collected in 4 cc K2 EDTA (purple top) tubes pre-dose, and at the following time points prior to drug administration on that day: cycle 1 day 15, C2D1, C3D1, and C4D1. One 4 cc EDTA (purple top) tube will be obtained for each time point. All samples will be centrifuged, and plasma will be separated and stored at –70°C for analysis. Depending on the initial results, sampling times may otherwise be adjusted, but neither the total number of samples nor the total amount of blood will be increased.

Plasma samples for PK analysis will be sent to the laboratory for extraction and analysis c/o:

Tracy W. Webb
Office of the Associate Director
Developmental Therapeutics Program
Frederick National Laboratory for Cancer Research Boyles Street Building 1047 - Room 8
Frederick, MD 21702

301-846-7402
wolfet2@mail.nih.gov