Clinical Center # 09-C-0192
CTEP # 8463

Phase II Study of Cediranib (AZD2171) in Patients with Alveolar Soft Part Sarcoma

Abbreviated Title: Ph II AZD2171 in ASPS

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NCI Supplied Agent	AZD2171 (NSC 732208)
IND number:	114163
Version date:	November 15, 2021
NCT Number:	NCT00942877

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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), a VEGF/KIT tyrosine kinase inhibitor, has recently demonstrated antitumor activity in early phase clinical trials, which included 7 adult and 3 pediatric patients with ASPS.

Objectives:

Adult patients:

- To determine the response rate (PR + CR) of AZD2171 in adult patients with ASPS.
- To compare gene expression profiles between pre-treatment and post-treatment biopsy specimens.

Pediatric patients:

- To determine if pediatric patients with ASPS will experience at least a minimal response rate when treated with AZD2171

Eligibility:

- Patients must have histologically or cytologically confirmed metastatic alveolar soft part sarcoma.
- <16 years old. BSA must be ≥ 1.04 m^2 and subject must be able to swallow tablets.
- Adequate organ function.

Design:

- Adult patients will be treated with AZD2171 at 30 mg by mouth once a day for 28 days (28-day cycles). Pediatric patients (<16 years old) will be treated with 12 mg/m^2/day once a day for 28 days (28-day cycles).
- Blood pressure will be monitored by a health care provider every 2 weeks for the first 2 cycles then at the start of every subsequent cycle (unless patients have experienced elevated blood pressure requiring drug therapy, or as clinically indicated).
- CT scans will be performed at baseline and every 2 cycles for restaging during the first 18 cycles. After 18 cycles, restaging CT scans will be performed every 3 cycles; after 36 cycles, restaging CT scans will be performed every 4 cycles; after 60 cycles, restaging CT scans will be performed every 6 cycles.
- The study will be conducted using an optimal two-stage design in both pediatric and adult patients. The portion in adults will rule out an unacceptably low 5% clinical response rate (PR+CR) in favor of a modestly high response rate of 25%. In pediatric patients, the study will rule out an unacceptably low 5% overall clinical response rate (CR + PR) in favor of a higher response rate of 35%.
- Optional biopsies will be performed in adult patients only at baseline and after 3-5 days of treatment (D3-D5) to evaluate early drug effect. A third optional biopsy after completion of 4 weeks of therapy (between C1D28 and C2D7) may be collected with the intention of providing further information about disease response to treatment. Depending on results of initial gene expression profiles, the timing of the biopsies may be adjusted, but without change in total number of biopsies per patient.
- In a retrospective pilot study, CT scans from 20 consecutive off-study patients will be re-reviewed. RECIST imaging measurements will be compared to volumetric density (Total Volume of Viable Tumor, TVVT) CT measurements. The objective is to establish whether volumetric density/percent necrosis algorithms such as TVVT more accurately assess extent of disease and response to therapy than standard RECIST criteria.
- The total accrual ceiling is 73 participants (60 adult and 13 pediatric patients).

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1 Study Objectives

1.1 Primary Objectives

Adult patients: (Study objectives met for adult cohort with Amendment K 02/01/13)

- To determine the response rate (PR + CR) of AZD2171 in adult patients with ASPS.
- To compare gene expression profiles between pre-treatment and on-treatment biopsy specimens.

Pediatric patients:

- To determine if pediatric patients with ASPS will experience at least a minimal response rate when treated with AZD2171.

1.2 Secondary Objectives

- Retrospectively compare volumetric density (Total Volume of Viable Tumor; TVVT) (all lesions; volume/density) vs. pre-determined RECIST (axial only).
- Correlate TVVT, RECIST, and treatment response.

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. It 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 [1], 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 [1-3].

The origin of ASPS remains unclear. ASPS 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. Results from a recent 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) [4]. Among the angiogenesis-associated transcripts were c-MET and vascular endothelial growth factor (VEGF). 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.

			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-06	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 [4].

ASPS has been termed a chemo-insensitive tumor, and finding an effective treatment for this rare, slow-growing disease remains a challenge [1]. 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 [5-7]. Reichardt et al. [3] 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 [8].

Interferon alpha-2b treatment of patients with ASPS was shown to be of some benefit [9-11], 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 [12].

Approximately 20 clinical trials are currently open to patients with ASPS, with 8 actively recruiting patients [http://clinicaltrials.gov]. These include oral perifosine (AOI Pharma, Inc; an alkyl-phosphocholine compound) at a dose of 100 mg daily until disease progression; ARQ 197 (ArQule; a novel small molecule drug) at 360 mg twice daily until disease progression; a vaccine against each patient's own tumor cells; radiation therapy; combination chemotherapy with doxorubicin and ifosfamide, and/or surgery; dasatinib (Bristol-Myers Squibb, an oral dual BCR/ABL and tyrosine kinase inhibitor) administered twice daily continuously in 28-day cycles; 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 AZD2171

AZD2171 (NSC 732208), an orally available small molecule, is a potent inhibitor of receptor tyrosine kinases (RTK), which influence the effects of a key angiogenic factor, VEGF. VEGF is implicated in tumor blood vessel formation and in disease progression in a wide range of solid tumor malignancies. Expression of this factor is increased by diverse stimuli, which include proto-oncogene activation and hypoxia, with the hypoxic state frequently occurring in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature and thereby potentially contributes to tumor progression—a leaky tumor endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumor cell migration during metastasis. With the goal of suppressing neovascularization and thus inhibiting tumor growth and metastasis, numerous antiangiogenic agents have been developed. In contrast to many of the intravenously administered antiangiogenic agents, a recently emerging class of novel, orally administered VEGF RTK inhibitors including AZD2171 has been developed [13] [14, 15].

Two high-affinity receptors for VEGF with associated RTK activity have been identified on human vascular endothelium, kinase insert domain-containing receptor (KDR; VEGFR2) and fms-like tyrosine kinase 1 (Flt-1; VEGFR1). Although the relative contributions of KDR and Flt-1 signaling in mediating tumor progression have not been elucidated, a number of studies

suggest that KDR performs a predominant role. AZD2171 is a potent inhibitor of both KDR (IC_{50} <0.002 μM) and Flt-1 (IC_{50} = 0.005 μM) and shows activity versus c-kit, platelet-derived growth factor receptor beta, and Flt-4 at nanomolar concentrations, with much less potent activity against other serine/threonine kinases studied. AZD2171 potently and selectively inhibits VEGF-stimulated human umbilical cord vascular endothelial cell proliferation with an IC_{50} of 4 nM [16]. These authors have also demonstrated the agent's profound inhibitory effect on vessel area, length, and branching at subnanomolar concentrations using a modified fibroblast/endothelial cell co-culture system. AZD2171's effects on hemodynamic parameters have been studied in an athymic rat xenograft model of human colorectal carcinoma (SW620) using perfusion-permeability dynamic contrast-enhanced magnetic resonance imaging (*pp*-DCE-MRI) [17]. This method clearly demonstrated that in this model, AZD2171 significantly reduced vascular permeability, by 80% (P<0.005), and vascular volume, by 68% (P<0.05).

2.2.1 *Nonclinical Efficacy*

The effect of AZD2171 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 AZD2171 orally (PO) at doses from 0.75 to 6 mg/kg/day (2.25-18 mg/m^2/day) in a constant volume of 0.1 mL/10 g body weight for 24 to 28 days. AZD2171 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 AZD2171 efficacy studies [18]. In experiments incorporating a vehicle control, AZD2171 (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 AZD2171 administration [19]. When dosed with AZD2171 (0.75 to 6 mg/kg/day PO) at the time early lesions started to develop, the number of tumor foci was not affected, but their growth was inhibited. When tumors were well established before AZD2171 was given (at doses of 3 and 6 mg/kg/day), dose-dependent growth inhibition occurred, as well as tumor regression.

2.2.2 *Nonclinical Pharmacology and Toxicology*

Nonclinical pharmacology and toxicology company-sponsored AZD2171 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 to 6 hours after PO dosing. Plasma concentrations and exposure are generally linear over the dose ranges studied in rats. AZD2171 is excreted in the feces (>70% of the dose) of rats, dogs, and cynomolgus monkey after both PO and intravenous administration. Fecal excretion was the predominant route of elimination (>70% of the dose) in the rat, dog, and

cynomolgus monkey after both oral and intravenous administration. Elimination was rapid in rats and monkeys with more than 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 AZD2171 concentration-time profiles obtained following a single oral dose indicated that systemic exposure increased in a greater than dose-proportional manner over the dose range 0.05 to 2.5 mg/kg.

Protein binding of AZD2171 was relatively high (90% to 95%) across all species examined and was independent of concentration (range: 0.03 to 10 mcg/mL) and gender. AZD2171 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 rats, dogs, and primates dosed with AZD2171; these pathologies are considered to be consistent with lesions induced by hypertension, although a direct effect by AZD2171 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).

AZD2171 did not induce rat hepatic microsomal P450 activity but caused a 40% to 60% reduction in CYP1A activity at the 2.5 mg/kg dose level. Inhibition studies *in vitro* using human hepatic microsomal protein gave IC_{50} values for AZD2171 against CYP2D6, CYP3A4 testosterone, and CYP3A4 midazolam of 32.9, 16.2, and 21.4 mcg/mL, respectively. For CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1, the IC_{50} values were outside the concentration range of AZD2171 examined. As the clinically relevant plasma concentration of AZD2171 has not yet been determined, any possible effect on compound clearance and drug interaction is currently unknown.

2.2.3 *Clinical Studies of AZD 2171*

The safety, tolerability, efficacy, and pharmacokinetics (PK) of AZD2171 have been evaluated in several Phase I and II monotherapy studies, the first of which was a Phase I study in patients with solid tumors and metastatic liver disease (Study 2171IL/0001) [20]. In addition, several Phase I and II studies have been conducted or are ongoing to assess the safety, tolerability, and efficacy of AZD2171 in combination with targeted or standard chemotherapeutic agents in patients with advanced cancer [21].

In Study 2171IL/0001, patients have received AZD2171 at doses ranging from 0.5 to 60 mg. Patient cohorts receive a single dose of AZD2171 followed by a 7-day washout period, then start a 28-day cycle of daily doses of the agent at the same dose level they received initially. AZD2171 was generally well tolerated at doses up to and including 45 mg/day [20]. The 60-mg dose of AZD2171 appears to be less well tolerated and is associated with increased adverse events, dose interruptions, and increases in serum thyroid stimulating hormone (TSH). The most frequently reported adverse events (AEs) in Study 2171IL/0001 were fatigue (47/83), diarrhea (39/83), nausea (34/83), dysphonia (30/83), hypertension (29/83), vomiting (26/83), and anorexia (24/83). Grade 3 or 4 drug-related adverse events were hypertension, hypertensive crisis, abnormal liver function test, hand-foot syndrome, and diarrhea. No clinically relevant changes in electrocardiogram parameters, heart rate, or laboratory parameters were observed.

AZD2171 PK data from Study 2171IL/0001 have established that following a single dose, AZD2171 is orally available with C_{max} ranging from 1 to 8 hours post dosing. Concentrations declined in an apparent bi-exponential manner thereafter with a $t_{½lz}$ ranging from 12.4 to 35.7 hours. Steady-state plasma concentrations were predicted by the single-dose PK with the grand arithmetic mean temporal change parameter value being 0.988. This observation supports the concept that there are no time-dependent PK changes. Dose proportionate increases in C_{max}, $C_{max,ss}$, AUC, and AUC_{ss} provide no evidence to reject linear PK for single and multiple AZD2171 doses ranging from 0.5 to 60 mg. The PK profile of AZD2171 supports once-daily oral dosing.

In the Phase I study in patients with solid tumors and metastatic liver disease (Study 2171IL/0001; N = 83), there were 2 confirmed partial responses and 22 patients with stable disease. Minor responses were observed in 2 patients with breast cancer and 1 patient each for colorectal, lung, head and neck, liver, and skin/soft tissue tumor types. Reductions in tumor blood flow and permeability were detected by DCE-MRI, and there were time- and dose-dependent decreases in VEGFR-2 levels. Data from this trial suggest AZD2171 is biologically active at doses of 20 mg and higher.

Although 45 mg was the initial recommended Phase II dose based on results from Study 2171IL/0001, subsequent studies have indicated that many patients are not able to tolerate this dose and require a dose reduction (Table 1) [21]. 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 [22, 23]. In one of these trials, 28 patients received AZD2171, and Grade ≥3 AEs included hypertension (5 patients at 45 mg, 8 patients at

30 mg), fatigue (5 patients), diarrhea (3 patients), vomiting (2 patients), hyponatremia (2 patients), oral cavity pain (2 patients), and nausea, constipation, abdominal pain, headache, and hypothyroidism (all 1 patient each); Grade 4 toxicities included CNS hemorrhage (1 patient at 45 mg), lipase (1 patient) and hypertriglyceridemia (1 patient) [22]. In the other trial, hypertension (33%) and fatigue (20%) were the most frequent Grade ≥3 AEs [23]. Similarly, in a Phase II study of AZD2171 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 [24]. Salient Grade 3 toxicities were fatigue (4 patients), proteinuria (2 patients), diarrhea, skin rash, transaminitis, muscle weakness, and hypertension (all 1 patient each). 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 AZD2171 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). Ryan et al. reported that AZD2171 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 [25].

In reference to this particular protocol and ASPS, the starting dose of 30 mg was chosen after review of the safety data from the Phase I and II trials sponsored by Astra Zeneca at the Royal Marsden Hospital, London, UK and the Christie Hospital, Manchester, UK. The clinical efficacy data which forms the basis for conducting this study (Section 2.2.4) is from the trials conducted by the group of investigators at these institutions. Patients with ASPS were unable to tolerate 45 mg for more than 1 to 2 cycles of therapy and then required dose modification for toxicity, particularly liver function test abnormalities. The starting dose was subsequently decreased to 30 mg; this dose was more tolerable with a manageable toxicity profile and for much longer durations. These observations were corroborated by Grade 3 elevation in transaminases within the first 2 weeks of a patient receiving AZD2171 by special exemption protocol at our institution, which resulted in dose reduction to 30 mg.

Table 1: Summary of Pertinent Clinical Trials With AZD2171 [21]

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.* (2008)	Phase I	Lung	RP2D = 30 mg (with cisplatin and gemcitabine)	8 /12 patients had grade III toxicities (hypertension, fatigue, diarrhea, voice changes); two had grade IV toxicities (one reversible CNS ischemia, one 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
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

DLT: Dose-limiting toxicity; FOLFOX: Folinic acid, fluorouracil and oxaliplatin; PSA: Prostate-specific antigen; RP2D: Recommended Phase II dose.

2.2.4 *Clinical Efficacy of AZD2171 in ASPS*

Efficacy and tolerability data were collected for 7 patients with ASPS (ages 26–49 years) treated with AZD2171; one patient was treated in a Phase II randomized trial of AZD2171 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. AZD2171 was administered orally once daily at an initial dose of 45 mg/day. Four patients had confirmed partial responses that have lasted for 169, 198, 226, and 352 days, respectively. Three patients have had prolonged disease stabilization lasting longer than 200 days. These data demonstrate an exciting activity profile for AZD2171 that supports further investigation in patients with ASPS (Figure 2).

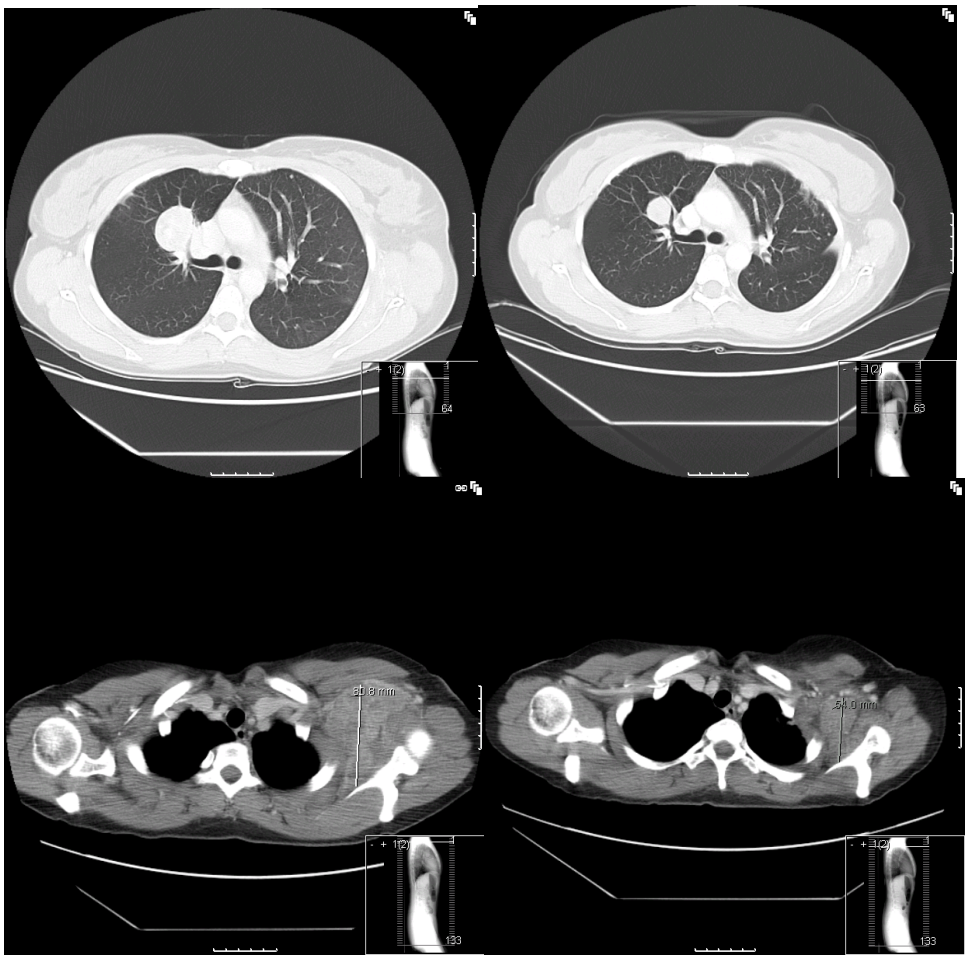

Figure 2: Pre- and post-treatment CT scans from a young woman with ASPS in the axilla and lungs treated with AZD2171 from August 2006 to June 2008.

The most frequently reported adverse events in patients with ASPS were similar to those reported in the other studies [20, 26]: fatigue (n=6), diarrhea (n=5), stomatitis (n=4), headache (n=3), and hypertension (n=3) [27].

2.2.5 *AZD2171 in Pediatric Patients With ASPS*

AZD2171 has been studied in 16 children (ranging from 8 to 18 years of age, median 15 years) with refractory solid tumors, excluding primary brain tumors, in a recently reported clinical trial [28]. The MTD was determined to be 12 mg/m^2/d (equivalent to 20 mg per dose based on a BSA of 1.8 m^2). Objective responses were observed in several patients with sarcomas, including Ewing sarcoma, osteosarcoma, and synovial sarcoma. Of the 3 patients with ASPS, one had prolonged disease stabilization and received more than 15 cycles of therapy.

This study will allow pediatric patients with ASPS access to AZD2171 to determine the activity in children <16 years of age. AZD2171 will be administered to all pediatric subjects at the pediatric MTD, dosed according to a standardized dosing nomogram (Appendix H).

2.2.6 *AZD2171 Clinical Toxicity*

Based on evidence from animal data with AZD2171 (vascular and renal pathology) and results in the ongoing Phase I clinical studies, it is possible that the agent will produce hypertension in man. Because hypertension seen in animals has been abrogated by nifedipine, the change is thought to be mechanistically related to inhibition of VEGF signaling, although a direct toxicologic effect on the blood vessels and kidneys cannot be ruled out. The potential for hypertensive changes following AZD2171 administration is additionally supported by evidence from use of other antiangiogenic agents in the clinic. For these reasons, patients will be monitored frequently for changes in blood pressure and renal function (blood urea nitrogen, creatinine, and urinary protein).

Certain physiologic processes other than endothelial cell growth are dependent on VEGF signaling, so inhibition of that growth factor may have implications for use of AZD2171 in selected patient populations. AZD2171 interferes with normal reproductive processes and completely prevents fetal development in rats at a dose of 2.5 mg/kg/day. For this reason, women of childbearing potential should have a negative pregnancy test before treatment with AZD2171 is initiated. In rat studies, AZD2171 significantly inhibited endochondral ossification and corpora lutea formation [29].

DLTs in the pediatric population included nausea, vomiting, fatigue, hypertension and prolonged QT interval. Non-dose limiting toxicities included left ventricular dysfunction, elevated thyroid stimulating hormone, palmar-plantar erythrodysethesia, weight loss, and headache [28]. Five out of 16 patients (30%) had non-dose limiting decreased left ventricular function (LVEF) during the first treatment cycle, and one patient had a grade 2 decrease in LVEF following cycle 2 [28]. In two patients, the LVEF improved within 4 weeks without intervention or dose modification.

Prior recommendations suggested that pediatric studies with AZD2171 be undertaken with caution because of the potential for increasing the zone of hypertrophy in the epiphyseal growth plates, thus preventing ossification during long bone growth. In the pediatric Phase I trial of AZD2171 [28], six patients had not achieved skeletal maturity at enrollment. In these patients, the median number of cycles administered was four (range, 2 to 15), and increase in height measured by triplicate stadiometer measurement during AZD2171 administration was 0.6 cm (range, 0 to 1.9 cm). No growth plate toxicity was identified in patients enrolled on this trial.

Pediatric patients in this study will be monitored closely for potential toxicity; in addition to adult monitoring parameters, height and weight analysis will be performed, and BSA calculations and frequent blood pressure evaluations will be monitored.

2.3 Rationale

There is no effective systemic treatment for patients with metastatic ASPS, but data from Phase II studies with AZD2171 supports further clinical investigation in patients with

metastatic ASPS[27]. Pediatric patients with ASPS will be enrolled to further evaluate clinical activity observed in the Phase I study of AZD2171 [28].

2.4 Trial Update

The results from this trial in adult patients with advanced ASPS were published in 2013 (Kummar et al. 2013). The objective response rate was 35% with 15 of 43 evaluable patients achieving a partial response (95% confidence interval: 21-51%) and 60% (26 patients) having a best response of stable disease. The disease control rate (partial response + stable disease) was 84% at 24 weeks. There were no responses in a 7-patient pediatric cohort of this study, for whom the best response was prolonged stable disease. This difference in response was considered potentially due to the maximum tolerated pediatric dose allowed being lower than the adult dose (Cohen et al. 2019). The protocol is closed to accrual. Two pediatric patients and one adult patient are continuing to receive cediranib after 59, 84, and 133 cycles, respectively.

2.5 Correlative Studies

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 [4, 30] 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 the VEGFR blocker AZD2171 in treating patients with ASPS, as well as our own data, merit further understanding of the mechanism of action of this therapeutic agent. 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 mechanism of action of AZD2171 by allowing detection of gene alterations as a direct consequence of AZD2171 effect and by comparing findings between responders and non-responders.

Tumor biopsies are not mandatory for participation in this protocol. For those willing to undergo biopsies, pre-treatment biopsies will be collected at baseline, and to try to detect early drug effect, a second biopsy will be performed between D3 and D5 of treatment and subjected to gene expression profiling. 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. A third optional biopsy after completion of 4 weeks of therapy (between C1D28 and C2D7) may be collected with the intention of providing further information about disease response to treatment. The timing of the biopsies may change depending on findings from gene analysis. However, the total number of biopsies per patient will not change.

2.6 CT Volumetric Density Assessment

The most widespread method of measuring metastatic tumor burden and treatment response in clinical trials, and the one used in this study (Section 11.1), is RECIST (Response Evaluation Criteria in Solid Tumors) [31]. RECIST uses 2D-proxies (single maximum diameter on axial images) to estimate tumor volumes. RECIST is limited in that it only assesses tumor response in terms of change in maximum axial dimensions in selected target lesions.

Furthermore, RECIST criteria may not be sufficient for metastatic tumor types such as ASPS, which frequently presents with extensive, highly vascular metastatic pulmonary lesions [32]. These metastatic lesions show subjective response on CT associated with reduced density and vascular/arterial perfusion (hypoattenuation) without the expected corresponding size reduction. This disproportional size reduction relative to clinical outcome may be a function of anti-angiogenic treatments, which may cause response via reduction of blood flow and necrosis in tumor that is not accounted for with current size-based tumor response criteria (Figure 3).

Recent studies in metastatic cancer imaging have demonstrated the added value of accounting for tumor density and volume using Size and Attenuation CT (SACT) [33], Mass, Attenuation, Size, and Structure (MASS) [34], or modified versions of the original Choi CT response criteria [35] beyond the axial dimensions provided by RECIST. In collaboration with investigators from the Department of Radiology and Imaging Sciences, we propose a more comprehensive tumor response method, Total Volume of Viable Tumor (TVVT), to quantify change in viable versus necrotic tumor volumes across all lesions through volumetric characterization of density distribution throughout all parts of all measurable tumors.

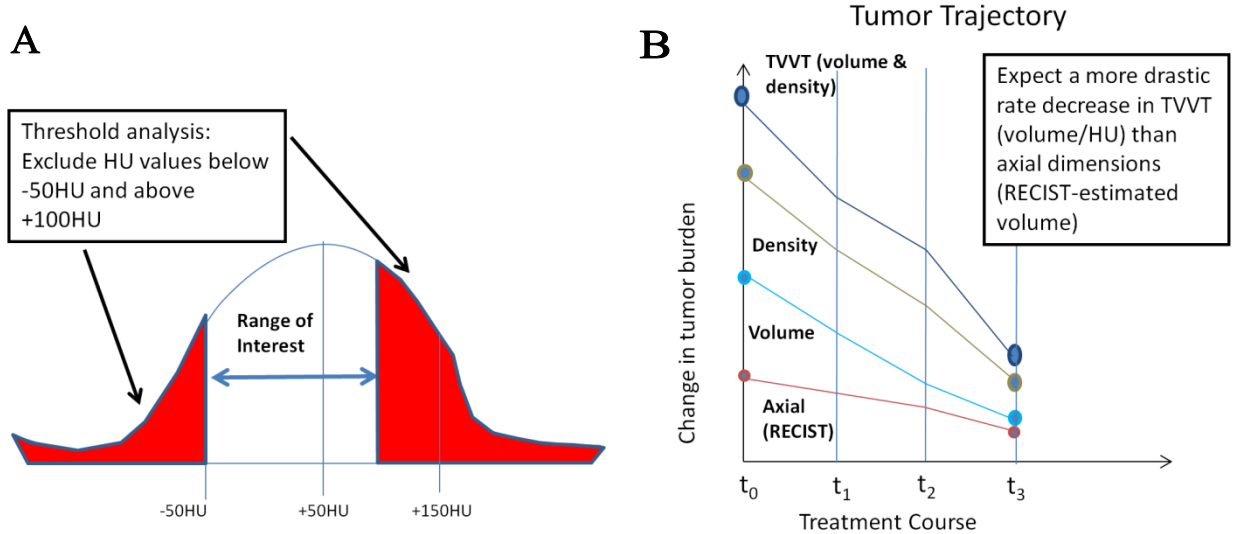

Figure 3**A**: Histograms can be used to calculate volumetric shifts in tumor composition and differentiate between necrotic and viable areas. Such use of thresholding can exclude areas not representative of tissues of interest (e.g., by excluding values over 100 Hounsfield units (HU) for calcifications and under -50HU for fat and artifact) giving a more comprehensive overall picture of tumor burden shift. **B:** Theoretical graphic representation of tumor trajectory over time in a

responding patient, demonstrating a more drastic decrease in TVVT (Total Volume of Viable Tumor, or volumetric HU) than axial dimensions on select lesions (RECIST); steeper declines may reflect treatment efficacy earlier than with RECIST.

In this retrospective pilot study, RECIST imaging measurements from 20 consecutive off-study patients will be compared to volumetric density (TVVT) CT measurements. The objective is to establish whether volumetric density/percent necrosis algorithms such as TVVT more accurately assess tumor response to treatment. No patient-related decisions will be made based on this assessment; applicable patients, who are all off study, will not be reconsented for retrospective data analysis.

3 Patient Selection

The adult cohort met study objectives and was closed to accrual with Amendment K, 02/01/13.

3.1 Eligibility Criteria

- Patients must have histologically confirmed alveolar soft part sarcoma. Pathology should be confirmed at the Laboratory of Pathology, National Institutes of Health.
- 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.
- Patients must have metastatic alveolar soft part sarcoma that is not curable by surgery. Patients who have surgically resectable tumors with metastasis will be considered on a case-by-case basis.
- 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 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 PI's discretion, and should have recovered to eligibility levels from any toxicities.
- Any degree of prior treatment is allowed, including other anti-angiogenic treatments (e.g., VEGFR2 inhibitors or bevacizumab). Patients with no prior therapy are eligible, provided they have metastatic disease that is not curable by surgery.
- BSA ≥ 1.04 m^2.
- ECOG performance status ≤2 for adults, Karnofsky performance status ≥ 50% for pediatric patients > 10 years of age, and Lansky performance status ≥ 50 for pediatric patients ≤ 10 years of age (Appendix A).
- Life expectancy of greater than 8 weeks.
- Patients must have normal organ and marrow function as defined below:

- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin <1.5 X institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal
- creatinine within normal limits based on age as follows:

Age (Years)	Maximum Serum Creatinine (mg/dL)
≤ 5	0.8
5 < age ≤ 10	1.0
10< age ≤ 15	1.2
> 15	1.5

OR

- creatinine clearance ≥60 mL/min for adults or ≥60 mL/min/1.73m^2 for children with creatinine levels above institutional upper limit of normal.

- QTc must be <500 msec.
- Pediatric patients: Normal left ventricular function with ejection fraction > 55% or shortening fraction ≥ 27%.
- At present, the potential of AZD2171 for clinically significant drug interactions involving the CYP isozymes is unknown. However, studies of the agent in rats indicated possible suppression of CYP1A that may be of biological significance. Eligibility of patients receiving any medications or substances known to affect or with the potential to affect the activity of PK of AZD2171 will be determined following review of their case by the Principal Investigator. Efforts should be made to switch patients with brain metastases who are taking enzyme-inducing anticonvulsant agents (Appendix B) to other medications one week prior to starting therapy.
- AZD2171 has been shown to terminate fetal development in the rat, as expected for a process dependent on VEGF signaling. For this reason, women of child-bearing potential must have a negative pregnancy test prior to study entry. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
- Ability to understand and the willingness to sign a written informed consent document.
- Patients should not be receiving any other investigational agents.
- Prior therapy with anti-angiogenic agents is permitted.

3.2 Exclusion Criteria

- Patients with clinically significant illnesses which would compromise participation in the study, including, but not limited to: active or uncontrolled infection, 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.

- Patients may not be receiving any medication that may markedly affect renal function (e.g., vancomycin, amphotericin, ibuprofen, pentamidine).
- Patients who are unable to swallow tablets.
- Mean QTc >500 msec (with Bazett's correction) in screening electrocardiogram or history of familial long QT syndrome.
- Greater than +1 proteinuria on two consecutive dipsticks taken no less than 1 week apart.
- Pregnant women are excluded from this study because AZD2171 is a VEGF inhibitor 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 AZD2171, breastfeeding should be discontinued if the mother is treated with AZD2171.
- HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for PK interactions with AZD2171.
- Adult patients with hypertension not controlled by medical therapy (hypertension defined as systolic blood pressure >150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management). Pediatric patients must have BP WNL for age. NOTE: blood pressure within the upper limit of normal is defined as: blood pressure ≤ the 95th percentile for age, height, and gender (Appendix I), and measured as described in Section 3.3.1, and not be receiving medication for treatment of hypertension.

3.3 Research Eligibility Evaluation

3.3.1 *Clinical Evaluations*

- A complete history and physical examination (including blood pressure, pulse, respiratory rate, and temperature) will be completed within 72 hours prior to the subject starting study drug. Patients <16 years old will have height and weight measured 3 consecutive times at baseline, and BSA calculated for dosing. Clinical evaluation will also include determination of performance status.
    - **Baseline blood pressure** in the pediatric patient is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:
        1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 5 minutes. Avoid using the lower extremity if possible.
        2) Average the systolic blood pressure from the 2nd and 3rd measurements.
        3) Average the diastolic blood pressure from the 2nd and 3rd measurements.
        4) The baseline BP is the average of the systolic over the average of the diastolic measurements.

- EKG will be done for determination of QTc within 72 hours prior to starting study drug.
- Pediatric patients: echocardiogram within 2 weeks of enrollment on study.
- Diagnostic imaging studies must be performed within 30 days prior to enrolling on study.

- PET scans will be done at baseline and, if clinically indicated, at restaging.
- After determining eligibility, pediatric patients will undergo lower extremity scanogram and unilateral knee MRI (if applicable) according to Appendix K.

3.3.2 *Laboratory Evaluations*

Baseline laboratory tests should be performed within 72 hours prior to receiving the study agents unless stated otherwise.

- Hematological profile: CBC with differential and platelet count
- Biochemical profile: electrolytes, BUN, creatinine, glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase, LDH
- TSH and T4
- Urinalysis
- Urine pregnancy test in women of childbearing potential

3.3.3 *Pathology Review*

A block or stained slides of primary tissue from the time of diagnosis 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 ASPS must be confirmed by the Laboratory of Pathology at the Clinical Center, NIH, prior to patient enrollment.

3.4 Patient Registration

Authorized staff must register an eligible candidate with the NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) (ncicentralregistration-l@mail.nih.gov). After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail.

3.5 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify the CRO when a patient is taken off protocol therapy and when a patient is taken off-study. The Participant Status Updates Form from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) (ncicentralregistration-l@mail.nih.gov).

4 Treatment Plan

This is a Phase II trial of AZD2171 in patients with ASPS.

4.1 AZD2171 Administration

The adult cohort met study objectives and was closed to accrual with Amendment K, 02/01/13.

Adult patients will receive 30 mg AZD 2171 tablets orally once a day in a 28-day cycle. AZD2171 will be available as 15 and 20 mg tablets. The dose of 30 mg daily has been shown to be safe in multiple Phase I and II trials of AZD2171 as a single agent. In the early phase trial that showed activity of AZD2171 in patients with metastatic ASPS, the initial dose of AZD2171 was 45 mg po each day. However, most patients required a dose reduction to 30 mg po each day due to associated toxicities. Dose modifications are outlined in Section 5.

Pediatric patients will receive 12 mg/m^2/dose (equivalent to 20 mg per dose based on a BSA of 1.8 m^2) according to the Pediatric Dosing Nomogram (Appendix H). Dose adjustments may be made based on changes in height and weight in pediatric patients at the time of restaging evaluations. If the pediatric patient is unable to maintain the study diary independently, the following instructions will also be presented to the parent(s).

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Patients will take AZD2171 on an empty stomach (either 1 hour before or 2 hours after meals). The drug will be administered once daily at approximately the same time each day. Tablets must be swallowed whole and not crushed. A new cycle may begin 1 day earlier or 1 day later than it would otherwise be scheduled based on the 28-day cycle, to allow for flexibility for days the clinic is closed and other unexpected events.

Note: For patient convenience, 2 cycles' worth of drug may be dispensed at a time to patients who have been on study for over a year and are tolerating treatment well. For patients who have been on study for over 18 cycles, 3 cycles' worth of drug may be dispensed; for patients who have been on study for over 36 cycles, 4 cycles' worth of drug may be dispensed; for patients who have been on study for over 60 cycles, 6 cycles' worth of drug may be dispensed.

Patients will be provided with a Study Diary (Appendix C), instructed in its use, and asked to bring it with them to each appointment. A new copy of the Study Diary will be given to patients whose dose is reduced due to adverse events. After cycle 2, a cycle will be considered completed if 90% of the prescribed doses are administered.

Blood pressure will be monitored every 2 weeks by a health care provider during the first 2 cycles, then at the start of each subsequent cycle (unless patients have experienced elevated blood pressure requiring drug therapy, in which case, the frequency of monitoring blood pressure will be determined by the study doctors and the patient instructed appropriately). Patients will be instructed to check their blood pressure at home more frequently.

CT scans will be performed at baseline and repeat imaging scans will be performed every 2 cycles during the first 18 cycles. After 18 cycles, CT scans will be performed every 3 cycles; after 36 cycles, every 4 cycles; and after 60 cycles, every 6 cycles. Patients may be

scanned earlier if clinically indicated. PET scans will be done at baseline and, if clinically indicated, at restaging.

Labs (CBC with differential, serum chemistries) will be performed every week for the first cycle, then every 2 weeks for cycles 2 and 3, and then at the start of each subsequent cycle. Physical assessment will be performed once per cycle for patients in cycle 2 onwards. For patients who have been on study for over a year up to 18 cycles (and are tolerating treatment well), physical exam/labs will only be performed once every 2 cycles/8 weeks. For patients who have been on study for more than 18 cycles up to 36 cycles, physical exam/labs will only be performed once every 3 cycles/12 weeks. For patients on study more than 36 cycles up to 60 cycles, physical exam/labs will be performed every 4 cycles/16 weeks. Patients on study more than 60 cycles will have physical exam/labs performed every 3 cycles/12 weeks, but every other exam/set of labs (when a CT scan is not required) may be performed by the patient's local physician. More frequent labs and assessment can be performed as clinically indicated. EKGs will be performed at baseline and as clinically indicated. ECHO/MUGA will be performed in adults as clinically indicated, and in all pediatric patients at baseline and serially thereafter (see Section 10).

Plain radiographs of tibial growth plates will be performed in all patients <16 years of age at study enrollment. Plain radiographs will be 2-view pictures: AP and lateral. Plain radiographs do not have to be performed in patients ≥ 18-years-old. In patients with open growth plates follow-up plain radiographs of the tibial growth plates will be performed as clinically indicated. Patients with evidence of open growth plates on plain radiographs will also have a growth plate (knee) MRI to further evaluate physeal pathology at baseline, and then after cycles 2, 4, 8, 12, and every 4th cycle thereafter.

Optional tumor biopsies will be collected prior to starting treatment on study (baseline) and then after completion of 3 -5 days of therapy (cycle 1, D3-D5) in adults only (the adult cohort has met study objectives and is closed to accrual. No biopsies will be collected on this protocol). A third optional biopsy after completion of at least 4 weeks of therapy (between C1D28 and C2D7) will be collected. Based on initial gene analysis results, the timing of the biopsies may change. However, the total number of biopsies per patient will not change.

Research biopsies will be performed only if minimal risk to the patient is estimated (Section 9.1.2). Determination of a disease site amenable to biopsy will be determined on an individual case basis after discussion with an interventional radiologist.

- All biopsies will be optional
- All biopsies will be by percutaneous approach
- No biopsy by an invasive (endoscopic, laparoscopic, or surgical) procedure will be performed.
- No visceral organ (ex. liver) biopsy will be performed, with the exception of lung.
- No core biopsies of lung lesions.
- Only fine needle aspiration (FNA) will be performed. FNA of lung lesions has been demonstrated to be safe. In a recent study, pneumothorax complication rate was < 10%, with only one patient out of 26 requiring a chest tube placement [36].

5 Dosing Delays/Modifications

5.1 Dose Modifications

Dose will be modified for grade 3 or greater non-hematologic toxicity (except electrolyte abnormalities unless these are not correctable within 48 hours) and/or grade 4 hematologic (except lymphopenia, anemia) toxicity. A maximum of 2 dose reductions will be allowed before the patient is taken off treatment. Patients who require a dose-reduction will not have the dose re-escalated. No more than 2 dose reductions will be allowed.

If administration of AZD2171 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).

5.1.1 Dose Modifications in Adults

All adult patients will be started on the initial dose of 30 mg po once per day for 28 days, in 28-day cycles.

Dose Modification table for adults:

Dose Level	Dose (mg/day)
1	30
-1	20
-2	15

Patients who tolerate the 30-mg dose for 2 cycles may, at the PI's discretion, have their dose increased to 45 mg [this was the initial dose used in the early-phase trial that showed activity in patients with ASPS, even though most patients required a dose reduction to 30 mg].

5.1.2 *Dose Modifications in Children (<16 years of age)*

All pediatric patients will be started on the initial dose of 12 mg/m^2/day (Appendix H) orally once per day for 28 days, in 28-day cycles. Dose adjustments based on changes in height and weight may be made every two cycles at the time of restaging evaluations when warranted (restaging CT scans will be performed every 2 cycles during the first 18 cycles; after 18 cycles, restaging CT scans will be performed every 3 cycles; after 36 cycles, restaging CT scans will be performed every 4 cycles; after 60 cycles, restaging CT scans will be performed every 6 cycles).

Dose Modification table for children:

INITIAL DOSE (mg/dose/day)	Reduced dose (mg/dose/day)	% Dose decrease from previous dose
30	20 mg/day	33

20	15 mg/day	25
15	15 mg/day daily for 5 days followed by 2 days rest *	29

*Patients who are receiving antihypertensive medication and require a dose reduction should take antihypertensive medication only on the days of cediranib administration. Antihypertensive medication should be held during the 2 rest days.

5.2 Dose Reduction

5.2.1 *Hematologic toxicities*

Dose will be modified for grade 4 hematologic toxicity (except lymphopenia, anemia) toxicity. AZD2171 should be held if the ANC is < 500/μL or the platelet count is < 50,000/μL during treatment. The study agent will be held until the ANC is ≥ 1000/μL and the platelet count is ≥ 75,000/μL (unsupported). Patients who experience any hematologic dose-modifying toxicity (DMT) should be treated at the next lower dose level according to Section 5.1 when sufficiently recovered from toxicity, for subsequent cycles.

5.2.2 *Non-Hematologic toxicities*

AZD2171 should be held in patients who experience grade 3 or greater non-hematologic toxicity until the toxicity returns to grade 1 or baseline, with the following exceptions. Doses will not be held for electrolyte abnormalities unless these are not correctable within 48 hours. Exacerbation of tumor pain can occur with administration of study drug; dose interruption/reduction will not be required for grade 3 or 4 tumor pain. Any patient who has a non-hematological dose-modifying toxicity that does not return to baseline within 14 days while holding drug will be removed from the study. Patients who experience non-hematologic toxicity should have appropriate laboratory testing at least weekly until the toxicity has resolved. Patients who experience any non-hematologic dose-modifying toxicity (DMT) should be treated at the next lower dose level according to Section 5.1 when sufficiently recovered from toxicity, for subsequent cycles.

5.2.3 *Hypertension toxicity*

Therapeutic blood pressure monitoring by a health care provider will occur every 2 weeks during the first 2 cycles, and then at the start of each subsequent cycle for the duration of treatment (unless patients have experienced elevated blood pressure requiring drug therapy). Table 2 will be used for the grading of AZD2171-associated hypertension in adults, for immediate and intermediate-term management, and for the determination of AZD2171 dose modification. An algorithm (Appendix J) will be used for the determination of dose modifications in pediatric patients experiencing dose-limiting toxicity (defined below) for the pediatric population (<16 years old).

Hypertension toxicity in the pediatric population:

Dose-limiting hypertension is defined as:

- A blood pressure >25 mmHg above the 95th percentile for age, height, and gender (Appendix I) confirmed by repeated measurement is dose-limiting (see Appendix J for management and grading).

- In patients on antihypertensive therapy, a blood pressure ≤ 25 mmHg above the 95th percentile for age, height, and gender (Appendix J) for > 14 days is dose-limiting (see Appendix F and Appendix J for management and grading).
- Grade ≥4 (CTCAE v.5) hypertension.

See Appendix E for instructions on collection and recording blood pressure information and Appendix F for suggested antihypertensive medications by class.

Table 2 outlines toxicity levels in adults based upon a level of elevated blood pressure (systolic and/or diastolic) recorded over a 72-hour period, based upon readings above the 95% for age, gender, and height. The schema of grade, intensity of anti-hypertensive therapy, duration of temporary discontinuation of AZD2171, reduction to the next lower dose level, or permanent discontinuation of drug are intended to allow appropriate, graded medical management for quantitatively graded levels of hypertension, only reducing dose (or ultimately discontinuing therapy) when recognized medical management is unable to restore blood pressure to 'normative' levels. Attention to Table 2 is critical in coding and managing this common complication of AZD2171 in the adult patient population.

Table 2: Management of Hypertension in Adults

BP measurements - systolic/diastolic	Interval	Treatment/Dose Modification
Patients **not** receiving maximal antihypertensive therapy:		
≥ 150 mmHg (systolic) **OR** ≥ 100 mmHg (diastolic)	2 BP readings at least 1 hour apart	• Add new or additional antihypertensive meds or increase dose of existing meds • Maintain dose of AZD2171
> 200 mmHg (systolic) **OR** > 110 mmHg (diastolic)	2 BP readings during a 1-week period	• Hold AZD2171 • Monitor patient closely for hypotension (if on antihypertensive meds) until AZD2171 is restarted. • Resume treatment when BP falls to <150/100
Patients receiving maximal antihypertensive therapy*:		
> 160 mmHg (systolic) **OR** > 105 mmHg (diastolic)	2 BP readings at least 1 hour apart	• Hold AZD2171 • Maintain antihypertensive meds and monitor patient closely for hypotension until AZD2171 is restarted. • Resume treatment at one lower dose level when BP falls to <150/100
* Maximal antihypertensive therapy is defined as four antihypertensive medications given for 2 weeks.		

Notes:

- While patients are receiving treatment with AZD2171, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 adverse event.

- Decisions to hold or decrease the AZD2171 dose during treatment must be based on BP readings taken in the clinic by a medical professional.

Appendix J outlines the toxicity levels in the pediatric population based on elevated blood pressure measurements repeated on the same day to confirm the elevation. As noted for the adult population, the schema of grade, initiation of anti-hypertensive therapy, duration of temporary discontinuation of study drug, and reduction to the next lower dose level or permanent discontinuation of drug are intended to allow for appropriate grading, management, and consistent safety measures in the pediatric patient population.

Management of Hypertension in Children (<16 yo): See Appendix J

An algorithm will be used to manage AZD2171-related hypertension (Appendix J). Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated (Appendix F). It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.

Notes:

- **Baseline blood pressure** is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:
  1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 5 minutes. Avoid using the lower extremity if possible.
  2) Average the systolic blood pressure from the 2nd and 3rd measurements.
  3) Average the diastolic blood pressure from the 2nd and 3rd measurements.
  4) The baseline BP is the average of the systolic over the average of the diastolic measurements.
- **Elevation** in either the systolic or diastolic blood pressure should be considered when following the algorithm (Appendix J).
  - **The upper limit of normal (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender (Appendix I).
  - CTC criteria (version 4.0) will be used to determine the grade of hypertension for reporting purposes.
  - Elevated BP measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.

5.2.4 *Proteinuria toxicity*

Evaluation of urine protein should occur weekly for the first cycle, every other week for cycles 2 and 3, and then once every cycle after if not previously abnormal. Table 3 defines the algorithm for patients with a positive urine dipstick.

Table 3: AZD2171 Dose Modifications for Proteinuria Toxicity Occurring after the First Six Weeks of Therapy

Proteinuria Value	Monitoring	Dose Modification
>1+ (dipstick or equivalent routine laboratory analysis)	Perform the following tests: • 24-hour urine collection for total protein and creatinine • microscopic examination of fresh urine	See below.
Based on results of the 24-hour urine collection:		
< 1g protein (24-hour collection)	Continue dipstick or equivalent routine laboratory analysis	Continue planned dose.
≥ 1g but ≤ 2g protein (24-hour collection)	Perform 24-hour urine collection (total protein, creatinine) prior to day 1 of each subsequent cycle of therapy (q4w) until total protein is <500 mg/24 hours	Decrease one dose level; continue treatment (only after the first six weeks of therapy).
>2g protein (24-hour collection)	Perform 24-hour urine collection (total protein, creatinine) weekly until proteinuria is < 2g	Hold AZD2171. When protein is < 2g/24 hours, resume treatment at one lower dose level (only after the first six weeks of therapy).
	Perform 24-hour urine collection (total protein, creatinine) prior to day 1 of each subsequent cycle of therapy (q4w)	Continue until patient is off study.

5.2.5 *Cardiac Toxicity*

For patients who develop compromised LVEF

1. Discontinue AZD2171 in patients who develop symptomatic heart failure;
2. Modify the AZD 2171 dose using the table presented in Appendix G in patients who develop compromised symptomatic LVEF. The NCI developed the table in Appendix G using the NSABP-B31 and NCCTG9831 monitoring guidelines for adjuvant trastuzumab in breast cancer. These studies enrolled populations considered most likely to be cured; thus, the investigators used the most stringent and conservative monitoring.

Note: Only 5 occurrences of compromised LVEF have occurred in 510 patients treated worldwide with AZD2171. Only a small portion of these patients are at increased risk based on the definitions provided in this protocol. Given the risk for and incidence of compromised LVEF secondary to AZD2171 treatment, this level of increased vigilance is sufficient.

5.2.6 *Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome*

RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with AZD2171 therapy (<3%). 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 AZD2171 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. AZD2171 should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. AZD2171 should be discontinued upon diagnosis of RPLS. After consultation with the principal investigator and CTEP, NCI, consideration of restarting the study may be evaluated in light of any clinical benefit.

5.2.7 *Growth Plate Abnormalities (pediatric patients)*

1D measurement through mid growth plate on sagittal view and volumetric measurements via an automated image analysis adapted from the MEDx software program used for volumetric analysis, will be used to measure growth plate changes. Growth plate expansion greater than 2 times the volume from baseline to interval measurement will be considered dose limiting. AZD2171 should be discontinued upon determination of dose limiting growth plate abnormalities.

5.3 General Concomitant Medication and Supportive Care Guidelines

All patients will be provided with the best available supportive care. At present, the potential of AZD2171 for clinically significant drug interactions involving the CYP isozymes is unknown. However, studies of the agent in rats indicated possible suppression of CYP1A that may be of biological significance. Efforts should be made to switch patients with brain metastases who are taking enzyme-inducing anticonvulsant agents (Appendix B) to other medications one week prior to starting therapy. The case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

5.3.1 *Anti-epileptic drugs*

Anti-epileptic drugs may be used, if indicated. Patients requiring a change in anticonvulsants once on therapy should be switched to an anticonvulsant with a similar effect on hepatic enzymes.

5.3.2 *Febrile neutropenia*

Febrile neutropenia should be managed according to the local institutional guidelines. Measures include laboratory testing, blood and urine cultures, and institution of broad spectrum antibiotics.

5.3.3 *Growth Factors*

Routine use of growth factors (i.e., Filgrastim, Sargramostim, Erythropoietin) is not permitted. However, therapeutic use of filgrastim or sargramostim in patients with serious neutropenic conditions, such as sepsis, may be considered at the investigator's discretion.

5.3.4 *Anti-emetics*

If a patient demonstrates the need for antiemetics, their use will be at the treating physician's discretion.

5.3.5 *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 + 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).

5.3.6 *Abnormal Thyroid Function*

The treatment of chemical hypothyroidism in patients that are asymptomatic continues to be at the discretion of the treating physician. Patients with symptoms consistent with hypothyroidism require replacement therapy. Currently, no standard is available regarding non-symptomatic patients although the endocrine services at the Dana-Farber Cancer Institute and St. Jude recommend treatment for patients with any degree of chemical hypothyroidism as defined by their laboratory profiles even without symptoms given the overall safety of thyroid replacement.

5.4 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,
- Intercurrent illness that prevents further administration,
- More than 2 dose reductions required for toxicity (as described in Section 5.1) or unacceptable toxicity
- 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.

5.5 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.

5.6 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 3.5.

6 Human Subjects Protection

6.1 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 are excluded from this 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.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	8	+	8	=	16
Not Hispanic or Latino	26	+	18	=	44
Ethnic Category: Total of all subjects	34 (A1)	+	26 (B1)	=	60 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	2	+	2	=	4
Black or African American	4	+	4	=	8
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	28	+	20	=	48
Racial Category: Total of all subjects	34 (A2)	+	26 (B2)	=	60 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

Accrual Rate: 4 pts/month **Total Expected Accrual:** 54 Min 60 Max

6.2 Justification for Exclusions

Pregnant women are excluded from this study because AZD2171 is a VEGF inhibitor 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 AZD2171, breastfeeding should be discontinued if the mother is treated with AZD2171. 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 AZD2171. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

6.3 Participation of Children

This study includes patients under 16 years of age. Given the recent results of the Phase I study in children [28], exploration of the activity in this patient population is warranted. Enrollment of children will be limited to those with a minimum BSA of 0.63 m^2 and those who are able to swallow tablets for safe dosing with AZD2171. Appropriate safeguards for toxicity monitoring, particularly for toxicity related to hypertension or effects on bone growth, are included in the protocol design.

6.4 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 protocol Section 6.6. 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.

6.5 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients or patient's parents or guardian if he/she is a child of the purpose, alternatives, drug administration plan, research objectives and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature 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. 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. Where deemed appropriate by the clinician and the child's parents or guardian, the child will also be included in all discussions about the trial and verbal or written assent will be obtained depending on the age of the child. The parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent.

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, all subjects ≥ age 18 at the NCI only 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 MEC Policy 87-4 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.

6.6 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.

Pediatric patients: This trial is open to children under 16 years of age. The primary risk to patients participating in this research study is as stated above. Therefore, this protocol involves greater than minimal risk to children, but presents the potential for direct benefit to individual subjects. As noted above, safeguards will be implemented for early detection and treatment of possible toxicities.

6.6.1 *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.

7 Adverse Events: List And Reporting Requirements

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

CAEPR for Cediranib (AZD2171, NSC 732208)

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

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

Version 2.15, November 7, 2018[1]

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

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%)**	
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lymphocyte count decreased		
	Neutrophil count decreased		
	Platelet count decreased		
	Thyroid stimulating hormone increased		***Thyroid stimulating hormone increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Generalized muscle weakness		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
	Lethargy		
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			

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%)**	
	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.

7.2 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.**).

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

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

7.2.2 Expedited Adverse Event Reporting

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

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

7.2.2.1 Expedited Reporting Guidelines

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

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

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

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

7.2.2.2 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

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

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).

7.2.2.3 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.2.2.4 Secondary Malignancy

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

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

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

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

7.3 NIH Reporting Requirements

Definitions

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

7.3.1 OHSRP Office of Compliance and Training/IRB Reporting Requirements

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.

7.3.2 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

7.3.3 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 Dr. Dahut at dahutw@mail.nih.gov and to NCICCRQA@mail.nih.gov within one business day of learning of the death.

8 Pharmaceutical Information

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

Other Names: cediranib maleate, AZD2171 maleate

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

Molecular Formula: $C_{25}H_{27}FN_4O_3 \cdot C_4H_4O_4$ **M W:** 566.59 (maleate salt), 450.52 (free base)

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

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

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

In addition to the active pharmaceutical ingredient, tablet excipients include mannitol, dibasic calcium phosphate anhydrous, sodium starch glycolate, microcrystalline cellulose, and magnesium stearate with a film coat containing hypromellose 2910, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide.

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

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

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

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

If the study sponsor determines appropriate, cediranib tablets may be administered as a dispersion in plain water. Liquids other than non-carbonated water should not be used and the tablets should not be crushed or ground. The following procedure is recommended by the manufacturer for patients who can swallow liquids:

> Drop the appropriate dose of cediranib tablet/s into a glass containing 50-60 mL non-carbonated water. Stir the tablet/s until dispersed in the water, about 10 minutes (no crushing). Swallow the liquid immediately after dispersion is completed. Any residue in the glass is mixed with a half glass of water and swallowed.

Potential Drug Interactions: Cediranib (AZD2171) clearance is primarily mediated by flavin-containing monooxygenase enzymes (FMO1 and FMO3) and UPDGT1A4. It is not a substrate of CYP450 enzymes. In vitro studies suggest that cediranib (AZD2171) is a substrate for P-glycoprotein (P-gp), 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 UPDGT1A4 or P-gp 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 UPDGT 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, P-gp, OATP1B1, OATP1B3, OCT2,MATE1, UGT isoforms 1A1, 1A4 and 2B7. Use caution in patients who are taking concomitant medications that are sensitive substrates although clinically relevant inhibition of any of these is considered unlikely. *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 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). The efficacy of hormonal contraceptives may be reduced while receiving cediranib and an additional non-hormonal method should be considered. Men study participants should use a condom while receiving cediranib and for at least one week after the last dose. Refer to the protocol document for specific guidance.

Toxicities: A list of the adverse events and potential risks associated with AZD2171 can be found in Section 7.1.

Availability: AZD2171 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

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

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

Agent Accountability: The Principal Investigator or a responsible party designate by the PI will retain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form per CTEP Policy and Guidelines for Accountability and Storage of Investigational Drugs (http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs).

Note: For patient convenience, 2 cycles' worth of drug may be dispensed at a time to patients who have been on study for over a year and are tolerating treatment well. For patients who have been on study for over 18 cycles, 3 cycles' worth of drug may be dispensed; for patients who have been on study for over 36 cycles, 4 cycles' worth of drug may be dispensed; for patients who have been on study for over 60 cycles, 6' cycles worth of drug may be dispensed.

9 Correlative Studies

Optional tumor biopsies will be collected 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 AZD2171 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 Tissue Sample Acquisition and Processing (Adult Patients Only)

With Amendment K (02/01/2013), the adult cohort closed to accrual. No biopsies will be performed on this study.

For tumor biopsy site other than lung, two to three cores will be obtained. Samples will be divided as follows. If two cores are obtained, one core will be preserved in RNAlater for gene expression profiling. The other core biopsy sample will be divided such that 1/3 of the biopsy is fixed in 10% buffered formalin and submitted to Surgical Pathology, CCR/NCI (Bldg 10, 2N212) for routine diagnostic review, and the other 2/3 is flash frozen, shipped to PADIS, and kept for future analysis. If only one core is obtained, it will be divided in two (such that one half will preserved in RNAlater, the remainder will be divided to provide material for flash freezing and for fixation in formalin for diagnostic review). If a third core is obtained, it will be flash frozen, shipped to PADIS, and kept for future analysis. For lung as site of tumor biopsy, an FNA sample only will be acquired and preserved in RNAlater for gene expression profiling.

9.1.1 *Timing of Biopsies*

Biopsies will be performed at the following times:

- Before starting treatment on study (baseline)
- Cycle 1, between Day 3 and Day 5
- A third optional tumor biopsy may be performed after completion of cycle 1 (between Cycle 1, Day 28 and Cycle 2, Day 7).

The timing of the post-treatment biopsies may be adjusted depending on initial gene expression profile results, but the total number of biopsies per patient will not change

9.1.2 *Biopsy Procedure*

Serial tumor biopsies will be obtained through Interventional Radiology by a percutaneous approach. With each biopsy, for sites other than lung, it is preferred that at least two core biopsies not less than 18 gauge in diameter and at least 1 cm in length are obtained; the maximum number of core biopsies obtained during one procedure will be three. Only percutaneous biopsies will be performed on patients with solid tumors. It is estimated that there will be between 2 to 5 million cells from each core biopsy. For lung, tumor tissue will be sampled by FNA. 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. 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. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant as determined by the investigators and Interventional Radiology.

All cases will be carefully reviewed with the interventional radiologists who have extensive experience in performing such procedures. Only if the procedure is considered to be low risk then we will proceed with tumor biopsy in a given participant. If the

participant refuses a tumor biopsy, he/she will still remain on study and receive study medication.

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. In case biopsy samples are unable to be obtained for a given patient, the patient will still remain on study and receive study medication.

9.1.3 *Laboratory Contact*

For patients enrolled at the NCI, 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: NCIPK-PDsupportgroup@mail.nih.gov; Pager: 102-12798; Phone: (301) 451-1169; 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. Instructions for tumor biopsy collection and processing can be found in Section 9.2.

9.1.4 *Processing of Patient Tumor Samples For RNA Analysis*

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. (N.B.: Before use, check for RNAlater precipitate in tubes: in the unlikely event it is present, heat tubes at 37^{o}C and agitate until completely dissolved).
- Maintain tubes upright
- Samples collected in the RNAlater can be held/stored at 2^{o}C to 4^{o}C OR room temperature until being shipped (within 48h).

- Ship via courier to:

  Curtis Hose
  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

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.

9.1.5 *Processing of Frozen Tumor Samples*

Biopsy samples will be transferred into a 1.5-mL pre-chilled cryogenic vials and the vial with the specimen will be immediately dropped into liquid nitrogen. Frozen biopsy samples will be stored in Dr. Robert Kinders' laboratory at PADIS for future analysis.

Robert J. Kinders, Ph.D.
Principal Scientist
PADIS, LHTP
Applied/Developmental Research Directorate
Frederick National Laboratory for Cancer Research
Bldg 431, Rm 129
Frederick, MD 21702-1201
Tel. 301.846.6410

9.2 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.

9.3 Human Data Sharing Plan

What data will be shared?
We will share human data generated in this research for future research as follows:
X De-identified data in an NIH-funded or approved public repository
X Identified data in BTRIS (automatic for activities in the Clinical Center)
X De-identified or identified data with approved outside collaborators under appropriate agreements

How and where will the data be shared?
Data will be shared through:
X An NIH-funded or approved public repository: clinicaltrials.gov
X BTRIS (automatic for activities in the Clinical Center)
X Approved outside collaborators under appropriate individual agreements
X Publication and/or public presentations

When will the data be shared?
X At the time of publication or shortly thereafter

9.4 Bony Toxicity Evaluation in Pediatric Patients

9.4.1 *Pretreatment Evaluation*

- Lower Extremity Scanogram (bilateral hip and lower extremity plain x-rays for leg length discrepancy, femur length measurement, and growth plate assessment) will be performed after study enrollment prior to the first dose of AZD2171.
- Plain radiographs of tibial growth plates in all patients <16 years of age at study enrollment. Plain radiographs will be 2-view pictures: AP and lateral. Plain radiographs do not have to be performed in patients ≥ 18-years-old.
- Unilateral Knee MRI (Appendix K): The knee MRI will only be required for patients with open growth plates on x-ray. The imaging protocol is outlined in Appendix K. No IV contrast will be used for the knee MRI studies. The knee MRI will be done at

the same time of the radiographic evaluation for disease and will add less than 0.5 hour of scan time.

9.4.2 *Follow-up Evaluation*

- Plain radiographs of tibial growth plates will be performed if clinically indicated.
- Unilateral knee MRI: Growth plate MRIs will be repeated in subjects with open growth plates after cycles 2, 4, 8 and 12 (then every 4th cycle).

10 Study Calendar

Screening evaluations are to be conducted within 72 hours prior to administration of protocol therapy unless otherwise indicated. Diagnostic imaging must be done within 30 days prior to the enrollment on study. The research team may perform additional safety/monitoring tests as clinically indicated.

		Cycle 1				Cycles 2 and 3				Cycle 4 and subsequent cycles				
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	Off Study[d]
AZD2171[a]		X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------												X
Physical exam/vital signs/weight/ performance status[b,m,]	X	X		X		X				X				X
EKG[c]	X													
Height[l]	X					X[m]								
Serum chemistry[d, m]	X	X	X	X	X	X		X		X				X
CBC w/diff, plts[e, m]	X	X	X	X	X	X		X		X				X
B-HCG[f]	X[f]													
Tumor measurements[g]	X	Tumor measurements are repeated as indicated below.												X
Urine dipstick or urinalysis for protein [h]	X	X	X	X	X	X		X		X				X
Echo/MUGA[i]	X													
Adverse event evaluation		X ----------												X
TSH and T4	X					X				X				X
Plain radiograph of tibial growth plate[j]	X									X				
Unilateral knee MRI[k]	X[l]									X[l]				

a: AZD2171: Dose as assigned administered orally, each day for 28 days (1 Cycle). Patients should keep a pill diary (Appendix C).

b: BP monitoring should be performed by a health care provider every 2 weeks during cycles 1 and 2 and then at the start of each subsequent cycle, or more frequently if clinically indicated.

c: At baseline and as clinically indicated.

d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

e: CBC (WBC, Hgb, Hct, platelets, ANC, % neutrophils, bands, lymphocytes).

f: Urine pregnancy test (women of childbearing potential).

g: CT scan will be done at baseline and repeat imaging scans will be performed every 2 cycles during the first 18 cycles; after 18, 36, and 60 cycles, patients will have repeat imaging performed every 3,4,

or 6 cycles, respectively. Documentation (radiologic) must be provided for patients removed from study for progressive disease. PET scans will be done at baseline and, if clinically indicated, at restaging.

h: If patient has significant proteinuria (>1+), obtain a 24 hour urine for protein and creatinine clearance.

i: ECHO/MUGA will be obtained in pediatric patients at baseline and then may be done every 2 to 4 cycles if clinically indicated.

j: All patients <16 years old at study enrollment: Lower extremity scanogram (bilateral bilateral hip and lower extremity plain x-rays for leg length discrepancy, femur length measurement, and growth plate assessment) will be performed after enrollment prior to initial dosing.

k: Unilateral knee MRI: knee MRI will only be required for patients with open growth plates on x-ray. The imaging protocol is outlined in Appendix K. No IV contrast will be used for the knee MRI studies. The knee MRI will be done at the same time of the radiographic evaluation for disease and will add less than 0.5 hour of scan time. It will be repeated after cycles 2, 4, 8, 12 (then every 4 cycles) for as long as the growth plate remains open.

l: Height should be repeated prior to every other cycle in children <16 years of age.

m: CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (up to 3 days prior), then weekly throughout cycle 1, biweekly throughout cycles 2 and 3, and at the start of each subsequent cycle (up to 8 days before start of new cycle). After 12-18 cycles on study: the physical exam, CT scan, and all protocol-required labs will be done every 2 cycles. After 19-36 cycles: physical exam, required labs, CT scan will be done every 3 cycles. After 37-60 cycles: physical exam, required labs, CT scan will be done every 4 cycles. After 60 cycles: physical exam and required labs will be done every 3 cycles, and CT scan will be done every 6 cycles; every other exam/set of labs (when a CT scan is not required) may be performed by the patient's local physician.

11 Measurement of Effect

Radiologic evaluation for tumor measurements will be performed at baseline within 30 days prior to enrollment and then every 2 cycles or as indicated above.

11.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]) [31]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

11.1.1 *Definitions*

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with AZD2171.

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.)

11.1.2 *Disease Parameters*

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

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/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

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.

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 or absence 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 when both methods have been used to assess the antitumor effect of a treatment.

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

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.

Ultrasound (US): 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.

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.

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. Progression of disease will be determined per RECIST criteria as outlined below.

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 LD.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum 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 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 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).

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for This Category Also Requires*:**
CR	CR	No	CR	>4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	>4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once >4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. 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.

11.1.4.3 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.

11.1.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that 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 recurrent disease is objectively documented.

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

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

All data will be collected in a timely manner and reviewed by the principal investigator and/or protocol chairpersons every 2 weeks. In addition, there will be weekly meetings with the investigators, research nurse, protocol chairpersons, and principal investigator to discuss patient issues, as well as important adverse events and trends in the data.

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.

12.3 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 exclusively to Collaborator(s), the NCI, and the

FDA, as appropriate. All data made available will comply with HIPAA regulations.

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:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   9609 Medical Center Dr
   Rockville, MD 20850
   FAX 240-276-7894
   E-mail: anshers@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.

13 Statistical Considerations

The primary objective of this study is to determine if AZD2171 will be associated with a modest response rate in patients with alveolar soft cell carcinoma. In addition, this study will determine whether pediatric patients with ASPS will experience at least a minimal response rate when treated with AZD2171. Data from a very limited number of patients with this disease suggest that this agent may have a potentially useful level of activity in this population [27, 28].

The study in adults will be conducted as an optimal two-stage Phase II trial (Simon R, Controlled Clinical Trials 10:1-10, 1989), to rule out an unacceptably low 5% clinical response rate (PR+CR; p0=0.05) in favor of a modestly high response rate of 25% (p1=0.25). 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 9 evaluable patients. If there are 0/9 responses, accrual stops. If there are one or more responses in the initial 9 patients, then accrual continues to a total of 24 patients. As it may take several weeks to determine if 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 1 or 2 of the 24 patients respond, then this is inadequate; if 3 or more of the 24 patients respond, then this is favorable. Under the null hypothesis (5% response rate), the probability of early termination is 63%.

Following completion of the initial cohort of 24 evaluable patients, the primary objective of the study will be to enroll patients onto a replicate cohort using the identical therapy as that administered to the initial 24 patients. This cohort will consist of 30 evaluable patients. The overall clinical response rate in these 30 patients will be determined. If the response rate is approximately 50%, the maximum confidence interval width will be +/- 19%. Following the enrollment of the 30 patients in the replicate cohort, the response rates from the original 24 evaluable patients will be compared to that of the replicate cohort. If the two cohorts have similar results, that is, if they do not differ with a Fisher's exact p-value of <0.30, then the results from both cohorts will also be combined and reported together as well as separately. The maximum confidence interval width with 54 patients would be +/- 14%.

Biopsies will be obtained from as many patients as possible in the replicate cohort. The specimens will be subjected to gene expression profiling, with the analyses conducted under the direction of Dr. Richard Simon, Chief, Biometric Research Branch, DCTD. VEGFR pathway analysis will also be undertaken. If there are up to 3 independent outcome measures evaluated, and if 15 patients are able to provide biopsy specimens pre-treatment as well as at one or two times following treatment, then there would be 85% power for each difference from baseline equal to 1.0 SD of the difference (effect size =1) to be detected, using a 0.017 alpha level paired t-test for each evaluation. The 0.017 level for each of three comparisons will permit the overall family of tests to be performed at the 0.05 level, using an assumption of a very conservative Bonferroni adjustment for multiple comparisons. If there are up to 6 comparisons, there would be 76% power for each comparison, as a minimum. In practice, comparisons may be made using a Hochberg adjustment, which is not as overly conservative as the Bonferroni adjustment. Also, a Wilcoxon signed rank test may be used instead of a

paired t-test if the differences from pre-treatment are not normally distributed ($p<0.05$ by a Shapiro-Wilks test).

The portion of the study in pediatric patients will be conducted as a small, optimal two-stage phase II trial (Simon R, Controlled Clinical Trials 10:1-10, 1989), in order to rule out an unacceptably low 5% overall response rate (ORR; p0=0.05), in favor of a higher response rate of 35% (p1=0.35). 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 6 evaluable patients and if 0 of the 6 have a response, then no further patients will be accrued. If 1 or more the first 6 evaluable patients (16.7% or more) have a response, then accrual would continue until a total of 12 evaluable patients have enrolled. As it may take several weeks to months to determine if a patient has experienced a 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 is 1 response in 12 patients, this would be an uninterestingly low response rate, while if there were 2 or more responses in 12 (16.7% or more) patients, then this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (5% response rate), the probability of early termination is 74%.

It is anticipated that 6 pediatric patients per year will enroll on this trial. Thus, it will take up to two years to complete enrollment of pediatric subjects. At the present time, approximately 40 adult patients have been enrolled in slightly greater than 2 years. The former accrual ceiling, based on two cohorts of adult patients, was 60 patients, and accrual of adult patients is expected to be completed within 2 years as well. To account for these additional evaluable pediatric patients, the accrual ceiling will be increased by 13 (12 + an allowance for 1 inevaluable patient). Thus, the accrual ceiling will be set at 73.

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Appendix A: Performance Status Criteria

PERFORMANCE STATUS CRITERIA *Karnofsky and Lansky performance scores are intended to be multiples of 10.*					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	**Description**	**Score**	**Description**	**Score**	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction.	100%	Normal, no complaints, no evidence of disease.	100%	Fully active, normal.
		90%	Able to carry on normal activity; minor sighs of symptoms of disease.	90%	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory, able to carry out light or sedentary work, e.g., light housework, office work.	80%	Able to carry on normal activity with effort; some signs or symptoms of disease.	80%	Active, but tires more quickly.
		70%	Cares for self, unable to carry on normal activity or do active work.	70%	Both greater restriction of, and less time spent in, play activities.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60%	Requires occasional assistance but is able to care for most of own needs.	60%	Up and around, but minimal active play; keeps busy with quieter activities.
		50%	Requires considerable assistance and frequent medical care.	50%	Gets dressed, but lies around much of the day; no active play; able to participate in quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40%	Disabled; requires special care and assistance.	40%	Mostly in bed; participates in quiet activities.
		30%	Severely disabled; hospitalization indicated, although death not imminent.	30%	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to a bed or chair	20%	Very ill; hospitalization necessary; active supportive treatment required.	20%	Often sleeping; play entirely limited to very passive activities.
		10%	Moribund, fatal process progressing rapidly	10%	No play; does not get out of bed
5	Dead	0%	Patient expired	0%	Unresponsive; Dead

Appendix B: 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	Depakote, Depakene
Zonisamide	Zonegran
Enzyme inducing anticonvulsant drugs (EIACD)	
Generic Name	*Trade Name*
Carbamazepine	Tegretol
Felbamate	Felbatol
Phenobarbital	Phenobarbital
Phenytoin	Dilantin
Primidone	Mysoline
Oxcarbazepine	Trileptal

Appendix C: Study Diary
Page 1

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 ___ pills (15mg) and___ pills (20 mg) each day. Please take the pill(s) on an empty stomach either 1 hour before or 2 hours after meals.
3. Record the date, the number of pills 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	# pills and when taken	Blood Pressure		Symptoms
			morning	evening	
	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 cycle _____

Physician/Nurse/Data Manager's Signature _____

Appendix C: Study Diary
Page 2

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 ___ pills (15 mg) and ___pills (20 mg) each day. Please take the pill(s) on an empty stomach either 1 hour before or 2 hours after meals.
3. Record the date, the number of pills 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	# pills and when taken	Blood Pressure		Symptoms
			morning	evening	
	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 cycle_____

Physician/Nurse/Data Manager's Signature _____

Appendix D: Patient Drug Interactions Handout and Wallet Card

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

Patient Name:	**Diagnosis:**	**Trial #:**	
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	Cediranib (AZD2171)

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:
Cediranib (AZD2171) interacts with certain enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

	Explanation
CYP isoenzymes	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. 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.
Protein transporters	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 P-gp, BCRP and MATE2-K which may affect the clearance of other drugs that are dependent on these transport proteins.

These are the things that you need to know:
The study drug cediranib, may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals

or supplements (*e.g.* St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

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 P-gp, BCRP 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 doctors or pharmacist to determine if there could be any side effects.
- Cediranib (AZD2171) may potentially reduce the effectiveness of hormonal contraceptives. Please check with your study provider about using contraception while on study treatment.
- Patients receiving Cediranib (AZD2171) are at increased risk of bleeding. If you are receiving anticoagulation therapy, you will be monitored more frequently.
- Make sure your doctor knows to avoid certain prescription medications.
- 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.

(Next page: Patient Drug Interaction Wallet Card)

Clinical Center # 09-C-0192
CTEP # 8463

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE EMERGENCY INFORMATION	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE DRUG INTERACTIONS	NIH NATIONAL CANCER INSTITUTE
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** Cediranib interacts with: CYP 3A4, 2D6, FMO and UGT1A4 which are needed to clear cediranib from the body; transport proteins P-gp, needed to move cediranib in and out of cells; and P-gp, BCRP and MATE2-K needed to clear other drugs from the body. Cediranib must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** **Study Drug(S):** Cediranib (AZD2171)	**Use caution and avoid the following drugs if possible:** ***Hormonal contraceptives***	Your healthcare providers should be aware of any medicines that are "strong inducers/inhibitors of FMO1, FMO3, UGT1A4 and P-gp." Cediranib (AZD2171) inhibits enzymes "CYP 2D6 and 3A4, transport protein, P-gp. BCRP and MATE2-K and is highly protein-bound." **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor. Version DEC/2019	
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov

Fold at dotted lines:

Appendix E: Blood Pressure Collection and Recording (Adult Patients)

General Guidelines
Frequency of monitoring: Blood pressure (BP) should be monitored by a health care provider every 2 weeks for the first two cycles of therapy, and then once each cycle. Patients will be instructed to check their BP at home more frequently. Patients with significant elevation in blood pressure requiring medications will continue to evaluate blood pressure twice a day. If blood pressure elevation occurs requiring drug therapy, the frequency of monitoring blood pressure will be determined by the study doctors and the patient instructed appropriately.

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 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 BP >95% for age, height, and gender for patients ages 1-16 (see Appendix I) and >140/90 for patients' ≥18 years of age] – record at time of hypertension diagnosis and at all subsequent visits:

- BP changes from baseline (or from previous assessment) (specify grade changes per Table 2)

- 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 2)
- 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 F: Adult Antihypertensive Medication List

Dihydropyridine calcium-channel blockers (DHP CCB)				
Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Nifedipine XL	30 mg po qd	60 mg po qd	90 mg po qd	CYP 3A4 substrate
Amlopidine	2.5 mg po qd	5 mg po qd	10 mg po qd	CYP 3A4 substrate
Felodipine	2.5 mg po qd	5 mg po qd	10 mg po qd	CYP 3A4 substrate + inhibitor
Selective β blockers (BB)				
Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Metoprolol	25 mg po bid	50 mg po bid	100 mg po bid	CYP 2D6 substrate
Atenolol	25 mg po qd	50 mg po qd	100 mg po qd	No
Acebutolol	100 mg po bid	200-300 mg po bid	400 mg po bid	Yes (CYP450 unknown)
Bisoprolol	2.5 mg po qd	5-10 mg po bid	20 mg po qd	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)				
Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Captopril	12.5 mg po tid	25 mg po tid	50 mg po tid	CYP 2D6 substrate
Enalapril	5 mg po qd	10-20 mg po qd	40 mg po qd	CYP 3A4 substrate
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd	Yes (CYP450 unknown)
Lisinopril	5 mg po qd	10-20 mg po qd	40 mg po qd	No
Fosinopril	10 mg po qd	20 mg po qd	40 mg po qd	Yes (CYP450 unknown)
Rarely used:				
Perindopril	4 mg po qd	none	8 mg po qd	Yes but not CYP450
Quinapril	10 mg po qd	20 mg po qd	40 mg po qd	No
Angiotensin II Receptor Blockers (ARBs)				
Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Losartan	25 mg po qd	50 mg po qd	100 mg po qd	CYP 3A4 substrate
Candesartan	4 mg po qd	8-16 mg po qd	32 mg po qd	CYP 2C9 substrate
Irbesartan	75 mg po qd	150 mg po qd	300 mg po qd	CYP 2C9 substrate
Telmisartan	40 mg po qd	none	80 mg po qd	Yes but not CYP450
Valsartan	80 mg po qd	none	160 mg po qd	Yes but not CYP450
α and β blocker				
Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Labetolol	100 mg po bid	200 mg po bid	400 mg po bid	CYP 2D6 substrate + inhibitor

Notation for management of pediatric patients with treatment-emergent hypertension

The algorithm in Appendix J will be used to grade and manage AZD2171-related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (consider a calcium channel blocker such as amlodipine or nifedipine) should be started, and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Appendix I.

Appendix G: 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 MUGA/ECHO within 1-2 cycles
1-5% below LLN	Continue and repeat MUGA/ECHO within 1-2 cycles	Continue and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles
≥ 6% below LLN	Continue and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles

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 MUGA/ECHO" or improves from a HOLD to a "Continue and repeat MUGA/ECHO" category, additonal MUGA scans/echocardiograms prior to the next scheduled MUGA/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 H: Pediatric Dosing Nomogram for AZD2171

Dose Level	Dose (mg/m^2/dose)				
1	12	BSA*	1.04-1.45	1.46-2.08	≥ 2.09
		Dose†	15	20	30

* BSA, body surface area in m^2.
† Actual dose in mg (tablets sizes 15 and 20 mg) administered once daily.
Note: Dose reductions for patients experiencing dose-limiting toxicities are outlined in Section 5.1.2.

Appendix I: Blood Pressure Levels for Children by Age and Height Percentile

Blood pressure (BP) levels for BOYS aged 1-17 years (only patients under 16 years of age are eligible for this protocol)

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.2.3 for definition of dose limiting hypertension, Appendix F and Appendix J for grading and management of hypertension, and Appendix F for medical treatment of AZD2171 related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Blood pressure (BP) levels for GIRLS aged 1-17 years (only patients under 16 years of age are eligible for this protocol)

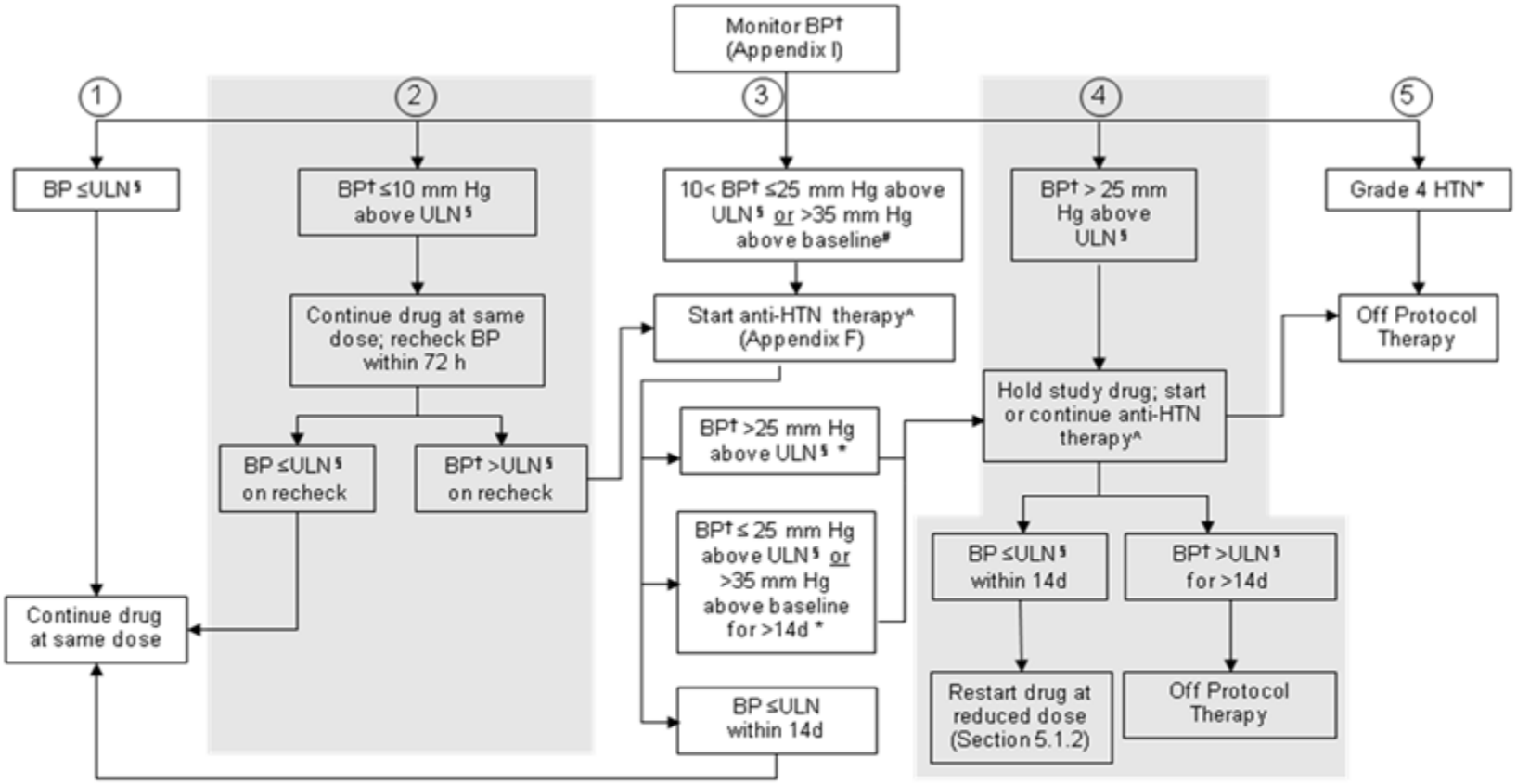
		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.2.3 for definition of dose limiting hypertension, Appendix F and Appendix J for grading and management of hypertension, and Appendix F for medical treatment of AZD2171 related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Appendix J: Blood Pressure Monitoring Algorithm in Children



Elevations in BP are based on systolic or diastolic pressures.

† Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.

§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix I)

* If BP >25 mm Hg above ULN for age (verified) or Grade 4 HTN at any time, hold drug. Study drug should also be held for BP ≤ 25 mm Hg above the ULN age for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.

^ Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

Baseline BP is defined in Section 5.2.3.

Directions for Algorithm:

Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95% for age, height, and gender, continue AZD2171 at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN for age, height, and gender, continue AZD2171 at the same dose and recheck the BP within 72 h.
  - If the BP is ≤ ULN on recheck, continue AZD2171 at the same dose.
  - If the BP remains above the ULN on recheck, then start antihypertensive therapy (Appendix F) and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started.

Arm 3 of algorithm:

- If BP is 11 to 25 mm Hg above the 95% for age, height, and gender on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start anti-hypertensive therapy (Appendix F), continue AZD2171 at the same dose, and monitor BP at least every twice weekly.
  - If the BP returns to ≤ ULN within 14 days, continue AZD2171 at the same dose and continue anti-hypertensive therapy.
  - If the BP remains elevated ≤ 25 mm Hg above the 95% or > 35 mm Hg above baseline for more than 14 days after the institution of anti-hypertensive therapy, hold AZD2171 monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that AZD2171 is held. The antihypertensive therapy should be continued until the BP is less than the ULN.
    - If the BP returns to ≤ ULN within 14 days, restart AZD2171 at a reduced dose (Section 5.1.2).
    - If the BP remains > ULN for more than 14 days, patient is Off Protocol Therapy.
  - If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, hold AZD2171, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that AZD2171 is held.
    - If the BP is ≤ ULN within 14 days, AZD217may be restarted at a reduced dose (Section 5.1.2).
    - If the BP is > ULN for > 14 days, the patient is Off Protocol Therapy (Section 5.4).

Arm 4 of algorithm:

- If BP is >25 mm Hg above the 95% for age, height, and gender, hold AZD2171, monitor BP and administer anti-hypertensive therapy as clinically indicated.
  - If the BP returns to ≤ ULN within 14 days, AZD2171 may be restarted at a reduced dose (Section 5.1.2).
  - If the BP is > ULN for >14 days, the patient is Off Protocol Therapy (Section 5.4).

Arm 5 of algorithm:

- If the participant develops Grade 4 hypertension (CTCAE), discontinue AZD2171, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy (Section 5.4).

Patients, who require a dose reduction of cediranib, which results in taking cediranib on days 1-5 followed by 2 days rest, should hold antihypertensive medication on the rest days when they are not taking cediranib.

Appendix K: Protocol for MRI Study of Knee

PATIENT ID NUMBER:_____

Note: Unilateral knee MRI. Right knee preferred over left unless prohibited by contractures, lesions, pain, or hypertrophy. This is done to examine the femoral and tibial growth plates. Only the series outlined below are required for the knee MRI for evaluation of femoral and tibial growth plates and must be performed within protocol specifications as indicated below. Two sequential scans of the knee will be performed per patient. The patient must step off the scanner and be placed back on the scanner between the two scans.

T1 Weighted Sagittal	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	72		
TR	500-600		
TE	min full		
Slice Thickness	3		
Bandwidth	20 kHz		
GAP	1.5 mm		
FOV	18		
FREQ	512		
Phase	256		
NEX	1		
PHFVO	Full		
Saturation	no FS		
OPTIONS	Fast		

Date:_____Signature (responsible MRI technician):_____

Appendix L: Therapeutic Response Assessment using CT Volumetric Density

Department of Radiology and Imaging Sciences investigator Dr. Les Folio and colleagues will retrospectively evaluate 20 consecutive off-study patients on Protocol 09-C-0192. All measurable lesions (>1.0 cm) will be assessed on baseline and follow-up CT. The specific aims are to:

1. Retrospectively compare TVVT (all lesions; volume/density) vs. pre-determined RECIST (axial only)
2. Correlate TVVT, RECIST, and treatment response

Registration and Lesion Management Application (algorithm/ software):
Automated registration and semi-automatic segmentation of all metastatic tumors >1.0 cm will be performed on serial CT scans using PACS (Picture Archiving and Communication System) Lesion Management Algorithm radiology imaging software (Carestream Health 11.3, Rochester, NY).

First, the baseline and follow-up CT scans are manually opened and globally registered to align axial planes between the two scans. The global registration algorithm employs a fully automated volumetric voxel-based rigid registration algorithm.[1] Second, tumors are manually located, which is performed by singly clicking on tumors, or by extending a measurement markup across conglomerated or abutting lesions. The PACS software then performs a refined registration by modifying the initial global registration dataset to enhance localization of the selected metastatic tumor across serial exams.[2] Next, the software automatically segments the target tumor on both CT scans using enhanced tumor edge detection (not necessarily defining separate lesions).[3] Finally, the PACS software automatically couples segmentation and tumor measurement, providing longest axial tumor length, perpendicular to longest axial length, short axis, mean HU density, and tumor volume of interest (VOI) in the segmented area. Observers then edit the typical segmentation outline using a freeform segmentation tool to exclude non-tumoral components.

All volume, size, and volumetric density measurements of the target tumors will be recorded on both the baseline and follow-up CT scans. All measurements will be performed by two observers (college graduates with no formal medical training) under other authors with over 10 years of experience in CT as body radiologists. The radiologists will verify observer segmentations, in consensus, when needed.

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1 Hawkes DJ. Algorithms for radiological image registration and their clinical application. J. Anat. (1998) 193, pp. 347-361.

2 Hong H, Lee J, Yim Y. Automatic lung nodule matching on sequential CT images. Comput Biol Med. 2008 May;38(5):623-34. Epub 2008 Apr 15.

3 Maintz JBA, Viergever MA. A survey of medical image registration. Med Image Anal 1998; 2:1–36.