Abbreviated Title: Phase II Axitinib in PHEO/PGL
CC Protocol #: 14-C-0001 G
Version Date: March 26, 2018
NCT Number: NCT01967576

Title: Phase II Study of Axitinib (AG-013736) with Evaluation of the VEGF-pathway in Metastatic, Recurrent or Primary Unresectable Pheochromocytoma/Paraganglioma

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Investigational Agents:

Drug Name:	Axitinib (AG-013736)
IND Number:	109,131
Sponsor:	Tito Fojo, M.D., PhD.
Manufacturer:	Pfizer Pharmaceuticals, Inc.

Commercial Agents: none

PRÉCIS

Background:

- Most treatments for malignant pheochromocytomas/paragangliomas (PHEO/PGL) are palliative and multidisciplinary. Chemotherapy using the combination of cyclophosphamide, vincristine, and dacarbazine has been successfully utilized in the management of rapidly progressive metastatic PHEO, with more than 50% complete or partial tumor response and more than 70% complete or partial biochemical response.
- VEGF expression and evidence of "angiogenesis" has been found in many PHEO/PGL, so it is plausible that interfering with VEGF signaling may result in anti-tumor activity in patients with PHEO/PGL.
- Axitinib (AG-013736) is an oral, potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3. *Pre-clinical data* suggests that the anti-tumor activity of axitinib may result from its "anti-angiogenic activity" and that this is reversible when treatment is discontinued.
- Given the known clinical safety and efficacy of axitinib, an assessment of its activity in PHEO/PGL and its impact on the VEGF pathway in PHEO/PGL could provide valuable information.

Objectives:

- Determine the response rate of metastatic PHEO/PGL to axitinib (AG-013736).
- Determine the progression-free survival of metastatic PHEO/PGL treated with axitinib (AG-013736).
- Explore the relationship of potential biological markers of axitinib activity with clinical outcomes.
- Perform pharmacogenomics analyses of drug metabolism and transport proteins through germline DNA examination.

Eligibility:

- Adults with a confirmed pathologic diagnosis of PHEO/PGL by the Laboratory of Pathology, NCI
- Biochemical evidence of PHEO/PGL
- Imaging confirmation of metastatic, locally advanced or unresectable disease.
- Measurable disease at presentation
- ECOG performance status ≤ 2
- Patients must not have received prior therapy with a tyrosine kinase (TK) inhibitor

Design:

- Phase II, open label, non-randomized trial
- Patients with metastatic pheochromocytoma/paraganglioma will receive axitinib (AG-013736 BID) in eight-week cycles
- Patients will be evaluated for response every twelve weeks (+/- 1 week) using RECIST criteria
- Approximately 12 to 37 patients will be needed to achieve the objectives of the trial

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To determine the response rate (RR) of metastatic or locally advanced pheochromocytoma/paraganglioma to axitinib administered daily

1.1.2 Secondary Objectives

- Determine the progression-free survival
- In an exploratory manner examine the extent of activation of the VEGFR pathway in pheochromocytoma/paraganglioma using a semi-quantitative immunohistochemistry assay and examine the relationship with response to therapy
- Perform pharmacogenomics analyses of drug metabolism and transport proteins through germline DNA examination.

1.2 BACKGROUND AND RATIONALE

1.2.1 Pheochromocytoma/Paraganglioma

Pheochromocytomas (PHEO) and Paragangliomas (PGL) are chromaffin cell-derived tumors that secrete and/or metabolize catecholamines. They are infrequent tumors occurring with an annual incidence of 3 – 8 cases per million per year in the general population. Its prevalence among patients with hypertension has been estimated to be 0.1 – 0.6%. Most tumors are sporadic, however approximately 25% of cases are associated with germline mutations in one of five major susceptibility genes. [1,2]

Clinical manifestations of PHEO/PGL are diverse, with similar symptoms occurring in other disease conditions. Most of the signs and symptoms are attributed to the direct actions of the catecholamines. These include hypertension, headache, palpitations, and anxiety. Hypertension can be paroxysmal or sustained. Some patients may present with orthostatic hypotension. [3] Biochemically silent tumors may be suspected from tumor mass effects or incidentally found on imaging studies.[4]

PHEOs are derived from the adrenal gland; PGL come from parasympathetic-associated tissues and from extra-adrenal sympathetic-associated chromaffin tissue. Both adrenal and extra-adrenal tumors show similar histopathological characteristics. The diagnosis of PHEO and PGL is based on the presence of symptoms, biochemical confirmation, and different imaging modalities. Biochemical testing is based on the continuous production of catecholamine metabolites and metanephrines.[5,6] Imaging procedures include anatomical and functional techniques.[3,7,8]

Malignant disease may occur in as many as 35% of patients with extra-adrenal PHEO and even more frequently in those with specific mutations. [9] Biochemical, morphological, and molecular markers have been investigated for use in the distinction of benign from malignant PHEO/PGL, but none appear to reliably indicate malignancy. Clinical criterion for malignancy is the presence of metastases, or presence of tumors in areas that normally do not contain chromaffin cells. [10]

PHEO metastasizes via hematogenous or lymphatic routes. Most common sites of involvement are lymph nodes, lung, bone, and liver. The frequency of malignant PHEO in certain genetic

disorders ranges from 1 to 90%. Metastases may be present at presentation or may occur later. [11] Succinate dehydrogenase (SDH) mutations are found in approximately 30% of patients with malignant PHEO/PGL.[12] Metastases to the liver and lungs are associated with a shorter survival. Overall, the estimated 5-year survival rates are between 34 and 74%.[11]

The clinical presentation of malignant PHEO/PGL is similar to benign tumors. Most common metastatic sites are local lymph nodes, bone (50%), liver (50%), and lung (30%). While histopathological characteristics of tumors may not show definite diagnosis of malignancy, clinical correlates, such as tumor weight > 80g, high tumor concentration of dopamine, tumor size > 5 cm, presence of confluent tumor necrosis, extra-adrenal tumor location, adrenal PHEO that do not take up metaiodobenzylguanidine (iobenguane, MIBG), persistent postoperative hypertension and a younger age have been associated with increased likelihood for malignancy. [13]

At present, most treatments for malignant PHEO/PGL are palliative and multidisciplinary. Pharmacologic management of functional component of the tumor is similar to that of benign disease. Surgical therapy can be used to potentially cure malignant disease; however, tumor dissemination limits the chance for a curative resection.[14] Other treatment modalities include cytoreductive techniques, radiopharmaceuticals, chemotherapy, radiotherapy, and experimental therapies. Targeted radiotherapy using 123-I MIBG is an option in systemic treatment.[15] Radiolabelled somatostatin analogues are being investigated.[16] Chemotherapy using the combination of cyclophosphamide, vincristine, and dacarbazine has been successfully utilized in the management of rapidly progressive metastatic PHEO, with more than 50% complete or partial tumor response and more than 70% complete or partial biochemical response.[17] External beam radiation, radiofrequency ablation, cryotherapy, microwave coagulation, and embolization have been used as well. [18,19]

1.2.2 The Genetics of Pheochromocytoma/Paraganglioma

Approximately 10-50% of cases may be hereditary. Hereditary PHEO/PGL is associated with multiple endocrine neoplasia type 2 (MEN 2), neurofibromatosis type 1 (NF-1), von Hippel-Lindau syndrome (VHL), and familial paraganglioma-pheochromocytoma caused by mutations in the genes encoding the components of succinate dehydrogenase complex (SDH). [20,21]

Multiple endocrine neoplasia type 2 is an autosomal dominant syndrome consisting of pheochromocytoma, medullary thyroid carcinoma and hyperparathyroidism.[22] The syndrome is caused by a mutation in the RET proto-oncogene located on chromosome 10.[23] The RET proto-oncogene encodes a glial cell line-derived neurotrophic factor (GDNF) that is specifically expressed in neural crest-derived cells such as catecholamine-producing chromaffin cells in the adrenal gland. [24]MEN2-associated PHEO are usually benign, localized to the adrenals, secrete epinephrine, and often present with paroxysmal hypertension.

Von Hippel-Lindau syndrome is caused by mutations in chromosome 3 encoding the VHL tumor suppressor gene.[25,26] VHL-associated PHEO typically develop according to Knudson's two-hit model: with an inherited germline mutation of VHL and a loss of function of the wild type allele. Pheochromocytoma developing in VHL has noradrenergic phenotype, with tumors located intra-adrenally, and is bilateral in about half of patients, with less than a 7% incidence of metastases. [27] Although the incidence of PHEO in VHL is low (about 1%), the presence of hypertension should prompt search for PHEO.[28]

Neurofibromatosis 1 is an autosomal-dominant condition. About 1-2% of patients with NF have a PHEO and about 5% of PHEO patients have NF. PHEO in NF is caused by germ-line mutations in the NF-1 gene. [29]

Familial PHEO/PGL syndrome is caused by mutations in the genes encoding the subunits of the succinate dehydrogenase (SDH) - SDHB, SDHC, and SDHD. The SDH enzyme is a complex consisting of four subunits and is located in the mitochondrial membrane without a cytosolic component. It plays an important role in phosphorylation and intracellular oxygen sensing and signaling.[30] Mutations in SDHB, SDHC, and SDHD were shown to cause pheochromocytoma-paraganglioma syndromes. [31] SDHD-associated PGLs have been observed in 4-7% of apparently sporadic PHEO with malignant disease occurring at a frequency < 3%. [32] SDHD mutations are associated with greater propensity to develop head and neck PGL and multiple tumors (mostly in the head and neck but also in the extra-adrenal abdominal, pelvic, and thoracic regions) with low risk for aggressive or malignant behavior. [33,34]

1.2.3 HIF-1a and VEGF Expression in Pheochromocytoma/Paraganglioma

One of the hallmarks for cancer formation is unregulated angiogenesis. In a search for histologic markers for malignancy in PHEO/PGLs, several studies have shown that tumoral vascularity is increased in malignant compared to benign PHEOs. [35,36] Utilizing immunostaining for Factor VIII and density of tumoral blood vessels has been shown to be increased in malignant lesions. Mean intratumoral microvessel density (using immunostaining with anti-CD31) in malignant pheochromocytomas is increased approximately two-fold as compared with benign tumors.[35]

Angiogenesis is a critical step in tumor growth and metastatic invasion. In a study of 19 PHEOs, induction of the genes for HIF1a, VEGF and VEGFR were found to be increased significantly in the malignant PHEO/PGLs.[37] Hypoxia-inducible factor 1 subunit alpha (HIF-1a) is a transcription factor involved in glycolysis and angiogenesis. In normoxemic conditions, HIF-1a is inactivated. In situations of hypoxia, HIF1a becomes stabilized, thereby initiating a cascade of events leading to induction of genes necessary for angiogenesis, such as VEGF.[38]

Vascular endothelial growth factor (VEGF) is one of the most important angiogenic factors involved in both tumor growth and metastasis. VEGF is a mitogen, a survival factor for vascular endothelial cells. Its receptor, VEGFR, is a tyrosine kinase and participates in the signaling mechanism for angiogenesis, vasculogenesis, vascular permeability, and endothelial cell motility among others. [39,40] In the study by Salmenkivi and others, VEGF expression was shown to be absent in normal adrenal medulla whereas it was found in all PHEOs studied, with moderate or strong immunoreactivity noted in the malignant tumors and only weakly positive to absent immunostaining in benign PHEOs. [41] In another study of surgical specimens of benign and metastatic human PHEO, VEGF expression was also shown to be significantly higher in metastatic human pheochromocytomas. [42] Xeno-transplanted PC12 showed marked VEGF expression and proliferation that were inhibited by anti-VEGF antibodies resulting in inhibited angiogenesis.[43]

Defects in the SDH gene causes hypoxia in the tumor cells leading to induction of hypoxia-inducible factors leading to promotion of angiogenesis. Mutations in the succinate dehydrogenase gene lead to succinate accumulation in the mitochondria and results in inhibition of HIF-1a prolyl hydroxylase stabilizing the HIF-1a subunit even in normal oxygen availability

leading to stimulation of angiogenesis that can promote malignant transformation and aggressive tumor behavior. [37]

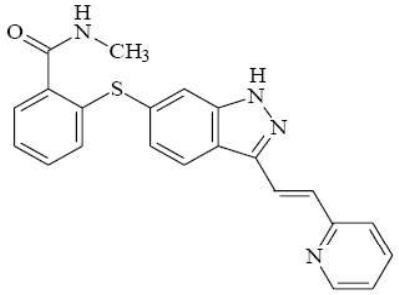
As of July 2013, there are 3 ongoing studies, evaluating antiangiogenic agents in malignant PHEO/PGL. These agents are all tyrosine kinase inhibitors (TKI): pazopanib (NCT01340794), sunitinib (NCT00843037) and dovitinib (NCT01635907).

1.2.4 Axitinib (AG-013736)

1.2.4.1 Molecular formula and chemical name

Axitinib is a small molecule with the molecular formula $C_{22}H_{18}N_4OS$: (**Figure 1**). The free base has a molecular weight of 386.47. The chemical name of the compound is N-Methyl-2-[3-((E)-2-pyridin-2-yl-vinyl-)-1H-indazol-6-ylsulfanyl]-benzamide

Figure 1: Structural Formula of Axitinib



Axitinib is white to light yellow crystalline powder.

1.2.4.2 Non-clinical studies

1.2.4.2.1 Primary pharmacodynamics

Axitinib is a small molecule adenosine triphosphate (ATP)-competitive inhibitor that binds to the unphosphorylated (non-activated) "DFG-out" conformation of the catalytic domain of a receptor tyrosine kinase (RTK).[44] This conformation is also known as the "deep pocket" or "back pocket" conformation and is occupied by the juxtamembrane (JM) domain of the receptor, when the latter is in the "DFG out" state.

Axitinib binds to this conformation while allowing the JM domain to simultaneously bind, uniquely interacting with the JM domain when compared to other inhibitors of the same class. In the published enzymatic assays, axitinib was found to be highly potent (inhibition constant [Ki] = 28 picomolar) against the kinase activity of JM domain containing human VEGFR2 recombinant (**Table 1**). In additional kinase assays, axitinib also showed potent and ATP-competitive inhibition of the RTK of VEGF receptors 1, 2, and 3, and platelet-derived growth factor receptor (PDGFR)-β, but not closely-related family kinases including fibroblast growth factor receptor 1(FGFR1), FMS-like tyrosine kinase 3 (Flt-3), tyrosine kinase endothelial -2 (Tie-2) and colony stimulating factor 1 (CSFR-1) (**Table 1**). Kinase activity screening with several broad kinase panels showed that axitinib was inactive against most kinases of distant families in the kinome. Thus the unique binding mode of axitinib in the kinase domain afforded its high potency and selectivity for VEGFRs.

Table 1: Enzyme Inhibitory Activities of Axitinib against Type III-V Family Kinases

Kinase	Ki (nM)[a] or % Inhibition at the highest compound concentration tested
JM Domain-containing VEGFR-2 kinase domain protein	0.028
VEGFR-2_FLVK	1.10
Phospho-VEGFR-2_FLVK	7.20
VEGFR-2-Kin	0.74
Phospho-VEGFR-2-Kin	21.7
FLK-1	81% @ 0.05μM
Phospho-FLK-1	40% @ 0.05μM
Flt-1 (VEGFR-1)	2.75
GST-PDGFR-β	1.27
CSF-1R	28.1
FGFR-1	47.6
Phospho-FGFR-1	56.7

[a] All data were fitted using tight-binding kinetic equations.

Phospho-: phosphorylated; FLVK: FGF-like VEGFR-2 kinase domain protein; Kin: kinase insert domain protein; FLK-1: mouse VEGFR-2 kinase domain protein; Flt1: Fms-like tyrosine kinase 1 (VEGFR-1) kinase domain protein; GST-PDGFR-□: GST fusion protein containing the amino acid residues between 558-1090 of PDGFR-□; CSF-1R: colony stimulating factor 1 receptor kinase domain protein; FGFR-1: fibroblast growth factor receptor-1 kinase domain protein.

In cell-based assays, axitinib inhibited VEGF-mediated auto-phosphorylation of VEGF receptors 1, 2, and 3 with a 50% inhibitory concentration (IC50) of 0.09-0.12 nM, 0.2 ± 0.06 nM and 0.1-0.29 nM, respectively. Axitinib had weaker inhibitory activity against PDGFR-α, PDGFR-β and stem cell factor receptor (KIT) with IC50 values of 5.0 ± 1.0 nM, 1.6 ± 0.4 nM and 1.7 ± 0.6 nM, respectively (**Table 2**). Axitinib did not potently inhibit the cellular activities of other RTKs tested, including CSF1-R, Flt-3, FGFR-1, rearranged during transfection [a receptor tyrosine kinase] (RET), epidermal growth factor receptor (EGFR), and mesenchymal-epithelial transition (cMet). Axitinib inhibited the survival of human umbilical vein endothelial cells (HUVECs) with an IC50 of 0.24 ± 0.09 nM and demonstrated approximately 1000-fold selectivity for VEGFR versus FGFR-1. Overall, in receptor binding studies and cell-based assays, it was concluded that axitinib is a potent and selective inhibitor of VEGF receptors 1, 2, and 3.[45] Axitinib dose-dependently inhibited endothelial cell (EC) tube formation derived from spheroidal ECs embedded in the 3-D fibrin matrix. Axitinib also inhibited VEGF-mediated EC adhesion and migration on extracellular matrix proteins and induced EC apoptosis as early as 6 hours after treatment in cell culture. In HUVECs, axitinib produced rapid and potent inhibition of endothelial nitric oxide synthase (eNOS), serine/threonine kinase (Akt), and extracellular signal-regulated kinases (ERK)1/2 phosphorylation at concentrations that correlated with its potency for VEGF receptors. In PDGFR-β-positive U87MG cells, axitinib dose-dependently inhibited platelet-derived growth factor (PDGF) -BB-stimulated cell migration, but not proliferation. Axitinib had little anti-proliferative effect on tumor cells that do not express VEGF receptors, PDGFRs, and/or stem cell factor receptor (KIT) receptor tyrosine kinases.

Table 2: Cellular Biological Properties of Axitinib

Assay	Cell Line	Stimulant	IC_{50} (nM)	IC_{50} (ng/mL)
Receptor Phosphorylation Assays				
VEGFR-2	VEGFR-2/PAE	VEGF-A	0.20 ± 0.06	0.08 ± 0.02
VEGFR-1	HUVEC	VEGF-A	0.09 - 0.12	0.03 - 0.05
VEGFR-3	VEGFR-3/PAE	VEGF-C	0.10 - 0.29	0.04 - 0.11
PDGFR-β	PDGFR-β/PAE	PDGF-BB	1.60 ± 0.4	0.62 ± 0.2
KIT	KIT/PAE	SCF	1.70 ± 0.6	0.66 ± 0.2
Receptor Phosphorylation Assays in Tumor Cells Lines				
Murine VEGFR-2	mVEGFR-2/ NIH3T3	VEGF-A	0.18 ± 0.03	0.07 ± 0.01
PDGFR-α	PDGFR-α/ NIH3T3	PDGF-AA	5.0 ± 1.0	1.9 ± 0.4
CSF-1R	CSF1-R/NIH3T3	M-CSF	73 ± 18	28 ± 6.8
Flt-3	RS;411	Flt-3 ligand	>1000	> 388
Growth Factor-Mediated Survival Assays				
VEGF-HUVEC[a]	HUVEC	VEGF	0.24 ± 0.09	0.09 ± 0.03
bFGF-HUVEC[a]	HUVEC	bFGF	238 ± 89	92.2 ± 34.4
VEGF-HUVEC[b]	HUVEC	VEGF	2.4 ± 0.9	0.93 ± 0.3
bFGF-HUVEC[b]	HUVEC	bFGF	2479 ± 1188	961 ± 460
Proliferation Assays in Tumor Cell Lines				
MV522 MTT	MV522	10% FBS	>10,000	NA
LLC MTT	LLC	10% FBS	>10,000	NA
M24met MTT	M24met	10% FBS	>10,000	NA

Note: All assays were performed in the presence of 0.045% BSA unless otherwise noted. IC50 values are expressed as average ± SEM, or a range if only two assays were performed.
BSA = bovine serum albumin; NA = not applicable; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay; M-CSF: macrophage colony stimulating factor; FBS: fetal bovine serum.
[a] Assay performed in the presence of 1% fetal bovine serum without BSA.
[b] Assay performed in the presence of 1% fetal bovine serum and 2.3% BSA.

1.2.4.2.2 In Vitro Activity of Major Metabolites of Axitinib

The major human plasma metabolites of axitinib include a sulfoxide (AG-028458 [also known as PF-03482595]) and an N-glucuronide (PF-04621675). In cells, the sulfoxide metabolite (AG-028458) had limited activity against VEGF receptors, PDGFR-β and KIT. In kinase counter screening assays, the sulfoxide metabolite only inhibited 2 kinases, Aurora-A and 5' adenosine monophosphate-activated protein kinase (AMPK), out of more than 100 kinases tested, with a >50% inhibition at the concentration of 1 µM; these biochemical inhibitory activities were also observed with axitinib. The N-glucuronide metabolite exhibited approximately 8300-fold less activity against VEGFR-2 auto phosphorylation and is assumed to have little activity against PDGFR and KIT based on computer modeling of the co-crystal structure.

1.2.4.2.3. Antiangiogenic Activity

Dynamic contrast enhanced- magnetic resonance imaging (Dce-MRI) studies showed that axitinib treatment decreased the overall tumor blood flow/permeability at as early as 2 days after initiation of treatment, with a maximum reduction in permeability surface area product (K^{trans}) observed on Day 7 after dosing. The change in vascular K^{trans} correlated with decreased microvessel density, cellular viability, and tumor growth.[46,47] Axitinib reduced tumor

microvessel density (MVD, measured by CD-31 staining) after either acute or prolonged treatment in multiple xenograft tumor models. In addition, reduction of MVD was associated with an increased tumor apoptosis and a reduction in tumor cell proliferation compared with the vehicle-treated tumors.[45]

In spontaneous pancreatic islet-cell tumors of RIP-TAG-2 transgenic mice and murine Lewis lung carcinoma in syngeneic mice, axitinib treatment (25 mg/kg, intraperitoneal (IP) or oral (PO), BID resulted in robust and rapid (within 24 hours after dosing) reduction in EC fenestrations, vascular sprouting, patency, and blood flow as well as decreased expression of VEGFR-2 and -3 in the remaining vessels.[48] Neo-angiogenesis occurred as early as 1 day after drug withdrawal and tumors were fully re-vascularized within 7 days, which responded to a 2nd cycle of axitinib treatment, suggesting that continuous daily dosing of axitinib may be optimal for anti-angiogenesis.[49] In the same model, the delivery of a targeting antibody that recognizes a tumor surface E-Cadherin to the ex-vascular space and the tumor cells were not affected by axitinib treatment.[50,51]

1.2.4.2.4. *In Vivo Anti-Tumor Activity*
Single Agent Activity

Axitinib was evaluated for its single agent anti-tumor activity in subcutaneously (SC) or orthotopic tumor models of colon, lung, kidney and liver in mice (**Table 3**). Axitinib consistently demonstrated anti-tumor activity in these nonclinical tumor models regardless of RTK expression status, consistent with its anti-angiogenesis mechanism of action. Overall, short-dosing breaks, following a loading dose treatment period, did not have significant negative effect on tumor growth inhibition (TGI). Additional studies showed that the anti-tumor efficacy of axitinib is not driven by Cmax, rather by adequate plasma exposure above the concentration for VEGFR target inhibition (Ctarget) over a prolonged period of time (**Table 4**).

Table 3: Anti-tumor Efficacy of Axitinib as a Single Agent in Mice

Disease Type	Model (Phospho-RTK Expression)	Description	Dose (mg/kg)	Regimen	Size at Start of Rx (mm^3)	Rx Period (Days)	TGI (%)
Human Colon Carcinoma	MV522 (None)	Dose-dependent TGI using axitinib	0.3	PO, BID	130	16	-20
			1				18
			3				15
			10				64
			30				61
			100				80
			150				95
			200				96
	HT29 (ND)	Dose response TGI	10	PO, QD	101	16	51
			30				76
			100				99
			150				99
	HCT-116-GFP (ND)	TGI (orthotopic implant)	30	PO, BID	One day after implant	10	nd
			30			17	87
			30			28	80
Lung Carcinoma	Murine LLC (PDGFR-β)	dose dependent efficacy	1	PO, BID	< 50	18	33
			3				49
			10				75
			30				68
			100				69
			300				Not tolerated
		TGI and anti-metastasis activity assessment	100	PO, BID (trocar implanted)	Prophylactic dose	38	73
			100	PO, BID (tail vein implanted)	--	survival	~ 11 days median survival
	Human SCLC (KIT^+)	Efficacy and dose response	30	PO, BID	180	16	47
			100				61
Human Renal Cell Carcinoma	SN12C-GFP (ND)	TGI (orthotopic implant)	10	PO, BID	Two days after implant	41	55
			10			72	61
			30			41	56
			30			72	74
			100			41	63
			100			72	70
Human HCC	Primary HCC tumor #LIMSH050 (ND)	TGI	15	PO, BID	140-160	26	54
			30	PO, BID			45

Axitinib was formulated in 0.5% carboxymethylcellulose (CMC)/H2O (wt/v) as a suspension formulation and dosed via oral gavage (PO). Tumor volumes were measured 2 - 3 times/week by electronic calipers and were calculated according to the equation of 0.5×[length×(width)2]. Animal body weight and health were assessed daily. Treatment usually lasted for 2-4 weeks or when tumor size(s) in the control group reached 1500-2000 mm3, TGI: tumor growth inhibition. TGI% was calculated as [1-(ΔTreated/ΔControl)]x100.

The anti-tumor efficacy of axitinib was compared to that of sorafenib in two human HCC xenograft models (MHCC97H and LIMSH050). Compared to the vehicle control group, axitinib (15 mg/kg, BID PO) significantly reduced primary tumor growth in both models; and in the MHCC97H model also suppressed lung metastasis and serum alpha-fetoprotein (AFP) (an indicator of liver tumor burden). In both models, axitinib showed similar anti-tumor activity and tolerability as sorafenib or the combination of sorafenib plus sirolimus. Finally, in a 28-day

dosing study with the MHCC97H model, axitinib appeared to be better tolerated than sunitinib (at their respective therapeutic doses), while statistically equivalent anti-tumor efficacy was observed between the two compounds.

1.2.4.2.5. Pharmacologically Active Concentrations for Target Inhibition and Duration of Action

Based on a series of studies using various xenograft tumor models, the pharmacologically active axitinib concentration for Ctarget was estimated as 0.1-0.49 nM (or 0.04-0.19 ng/mL, unbound). This translates to a human Ctarget of 24-98 nM (or 9.3-38 ng/mL, total plasma concentration), assuming a 99.5% human plasma protein binding.

The pharmacologically active dose (ED50) in mouse, was estimated to be 8.7 ± 1.6 mg/kg, BID. The ED70 and ED80 were 30 mg/kg and 60 mg/kg (BID), respectively. The total efficacious concentration (Ceff) for humans was estimated to be 56-170 nM, or 22-66 ng/mL. (**Table 4**)

Table 4: Summary of IC50 and EC50 Values from Various Assays and Determination of target and Ceff of Axitinib

Method	Phamacodynamic End Point	Effective Concentrations (unbound)				Pharm Active Conc (unbound)	Total Pharm Active Conc for Human**	Designation
		IC_{50} (nM)	IC_{50} (ng/mL)	EC_{50} (nM)	EC_{50} (ng/mL)			
Cellular receptor phosphorylation via ELISA using transfected PAE cells	VEGFR2 phosphorylation	0.2	0.08			0.10 - 0.49 nM or 0.04 - 0.20 ng/mL	20 - 100 nM or 8.0 - 40 ng/mL	C_{target}
	VEGFR1 phosphorylation	0.1	0.04					
	VEGFR3 phosphorylation	0.29	0.11					
ocular angiogenesis model in developmental rats	Rat VEGFR2 phosphorylation			0.49*	0.19			
VEGF-mediated skin vascular permeability in mice	quantification of Even's blue dye in skin of mice			0.46	0.18			
In vivo EC50 derivation based on Cmin	TGI via PO, BID dosing (8 hr apart) in MV522			0.28	0.11	0.28 - 0.85 nM or 0.11 - 0.33 ng/mL	56 - 170 nM or 22 - 66 ng/mL	C_{eff}
In vivo EC50 derivation based on Cave	TGI via PO, BID dosing (8 hr apart) in MV522			0.85	0.33			
In vivo EC50 derivation based on Css	TGI via continuous minipump infusion in MV522			0.65	0.25			

* assuming rat plasma binding is 98%; ** Mouse plasma protein binding is 98%, human plasma protein binding is 99.5%; Mol Wt = 386 dalton

1.2.4.3 Clinical Studies

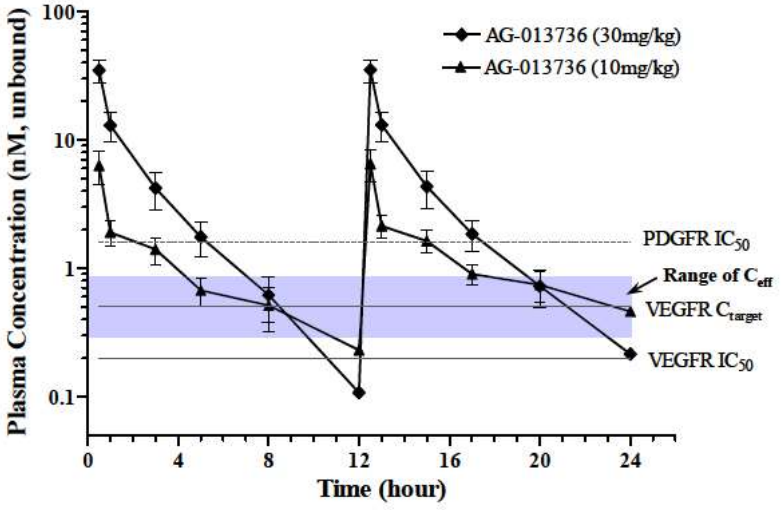
1.2.4.3.1 Pharmacodynamics

The analysis of C (plasma exposure) against T (length of exposure) for the 10 mg/kg BID dose level (~ ED50) of axitinib concluded that a 50% TGI can be achieved with the exposure period of ≥10 hours/day, ≥16 hours/day, or 24 hours if the unbound trough concentration of axitinib reaches ≥ 0.85 nM, ≥ 0.65 nM or ≥ 0.28 nM, respectively (the corresponding total concentration

for human is 66 ng/mL, 50 ng/mL or 22 ng/mL, respectively). The analysis also showed that inhibition of PDGFR-β by axitinib was transient at 10 and 30 mg/kg, and probably only played a minor role in anti-angiogenesis and anti-tumor activity of axitinib (**Figure 1**). This result is supported by the fact that only the high dose of axitinib (100 mg/kg) was able to produce a significant (90%) and sustained (>7 hours) inhibition of PDGFR-β phosphorylation in the C6 rat glioma model known to secrete PDGF and express high levels of active PDGFR-β, and that the 10 or 30 mg/kg dose levels of axitinib only produced partial and transient inhibition of PDGFRβ.

The efficacious human dose of axitinib was predicted by pharmacokinetic-pharmacodynamics (PK-PD) modeling using data from a MV522 TGI study and human pharmacokinetic (PK) parameters determined in Phase 1 clinical studies.[52] The modeling and simulation results predicted that 5-10 mg BID axitinib would result in a 40-60% TGI inpatients, assuming the pharmacodynamics (PD) parameters in patients are similar to those in MV522 tumors in mice.

Figure 2: Concentration and Time of Exposure Correlative Analysis for the Determination of Duration of Action for Axitinib



The duration of action against VEGFRs and PDGFR-β was assessed based on analysis of the plasma concentration/time of exposure relationship. Axitinib preferentially inhibited VEGFRs at the ED50 and ED70 doses. The PK profile was created by plotting plasma concentrations (± SEM) against time points of treatment with axitinib at 10 and 30 mg/kg and analyzed against values of the highest predicted Ctarget (0.49 nM) and the range of Ceff (0.28 – 0.85 nM, shaded area) of the compound. The IC50 values for VEGFR-2 (0.2 nM) and PDGFR-β (1.6 nM) are also shown. Axitinib was dosed PO, BID, 8 hours apart. The 12 hour concentrations were calculated based on the WinNonlin analysis of the PK. Accordingly, PK values between the 12 hour and 24 hour time frame were corrected using the estimated 12 hour plasma concentrations.

1.1.1.1.2 Clinical Safety and Efficacy

As of 1 June 2012, 43 studies evaluating the safety, efficacy, and PK of axitinib have been "completed"(C) or are "ongoing" (O): "Completed" signifies that the analysis for the primary endpoint has been completed and a clinical study report (CSR) is available; however, subjects may still be receiving treatment under the same protocol and may be being followed up for efficacy and safety. "Ongoing" signifies that the analysis for the primary endpoint has not been completed and a CSR is not available.

These studies include 15 Phase 1 studies in healthy subjects (including 1 study in patients with hepatic impairment) and 28 studies in 2543 subjects with cancer treated with axitinib including 1 continued access and 1 compassionate use study.

In the first Phase 1 dose-finding study (Protocol A40600010), thirty-six subjects with advanced solid tumors were treated with starting doses of 2 to 30 mg BID of Axitinib in 6 cohorts of 4 to 8 subjects each. The primary dose-limiting adverse event (DLT) was hypertension at starting doses > 5 mg BID. Other DLTs included diarrhea, stomatitis, and elevation of liver transaminases. A significant food effect was observed, with a higher rate and extent of absorption following overnight fasting. The recommended Phase 2 starting dose was determined to be 5 mg BID (without food or drink 2 hours before and after each axitinib dosing) [20]. Based on these finding from the first in human (FIH) Phase 1 study (Protocol A40600010), the initial Phase 2 studies in cancer patients were initiated with the recommendation that axitinib be administered with fasting two hours before and two hours after dosing. Of fourteen subjects treated at the MTD, two experienced DLTs (Grade 2 stomatitis and Grade 3 diarrhea.

Hypertension seemed to be the main DLT. Grade 1-3 hypertension was observed in six subjects, which was not dose-limiting and was managed with standard antihypertensive medications. All other treatment-related AEs at the 5-mg BID dose level were of Grade 1 or 2 in severity, with the exception of one subject who experienced Grade 3 dysphagia.

Among the first ten patients in the Phase 1 study who received doses up to six times the MTD of 5 mg BID (starting dose), two subjects with non-small cell lung cancer (NSCLC) cavitated their lung lesions and died of haemoptysis. Both subjects had adenocarcinoma, one with a centrally-located lesion and the other with a peripheral-located lesion. Both subjects received a starting dose of 20 mg BID. One patient's haemoptysis was considered to be related to axitinib.

Hypertension was noted in all of the first ten subjects, and five were Grade 3 or 4 in severity. Two subjects (receiving 10 mg BID and 20 mg BID as the starting dose) had seizures associated with hypertension and both recovered without sequelae. No home monitoring of blood pressure was done at the time.

Pharmacokinetics

Axitinib plasma pharmacokinetics was moderately variable, but exposures were generally dose proportional up to 15 mg daily dose. Axitinib has good oral bioavailability; a study in healthy volunteers indicated that the mean absolute oral bioavailability of the drug was 58%. An interaction study in healthy volunteers indicated that ketoconazole produced 2-fold increase in axitinib plasma exposures and a 1.5-fold increase in peak plasma concentration.

A study in healthy volunteers (A4061007) indicated that the mean absolute oral bioavailability of the drug was 58%. Interaction studies in healthy volunteers with the CYP3A4/5 inhibitor ketoconazole (A4061004) and CYP3A4/5 inducer rifampin (A4061026) produced a 2-fold increase and 79% reduction in axitinib plasma exposures, respectively. Axitinib has two major (non-pharmacologically active) circulating plasma metabolites, a glucuronide product and a sulfoxide product (A4061003). In subjects with moderate hepatic impairment (Child Pugh B), there was a ~2-fold increase in axitinib area under curve from zero to infinity (AUC (0-∞)) and a 1.3-fold increase in axitinib maximum plasma concentration (Cmax) compared to subjects with normal hepatic function (A4061036). No difference in axitinib plasma pharmacokinetics was observed between Caucasian and first-generation Japanese volunteers (n=20 each) (A4061026).

Phase 1 studies in combination with chemotherapeutic/anticancer agents in cancer patients have indicated plasma pharmacokinetics of docetaxel, paclitaxel, carboplatin, capecitabine, gemcitabine, cisplatin, pemetrexed, oxaliplatin, 5-fluorouracil (5-FU), bevacizumab, and irinotecan (including its SN-38 activated metabolite) were similar in the absence and presence of axitinib. Likewise, axitinib plasma profiles and pharmacokinetic parameters were similar in the presence and absence of these co-administered chemotherapeutic/anticancer agents

A pooled population pharmacokinetic analyses using data from 17 clinical studies that included healthy volunteers (n=338) as well as patients (n=207) with solid tumors (including patients with advanced RCC) indicated that there are no clinically relevant effects of age, gender, body weight, race, renal function, and UGT1A1 and CYP2C19 genotype on axitinib plasma exposure. In addition, no apparent difference in pharmacokinetics between patients with advanced RCC and healthy volunteers was noted.

Safety

Overall, the adverse events reported in axitinib clinical studies are considered manageable, were generally reversible and expected for this class of agents. For single-agent axitinib, the most common adverse events reported from 699 cancer subjects regardless of causality included diarrhea (397 subjects, 56.8%), fatigue (368 subjects, 52.6%), hypertension (318 subjects, 45.5%), decrease appetite (286 subjects, 40.9%), nausea (264 subjects, 37.8%), dysphonia (242 subjects, 34.6%), palmar-plantar erythrodysesthesia syndrome (202 subjects, 28.9%), weight decreased (197 subjects, 28.2%), vomiting (166 subjects,23.7%), constipation (165 subjects, 23.6%), headache (151 subjects, 21.6%), cough (149 subjects, 21.3%), arthralgia and dyspnea (140 subjects, 20%). Additionally, hypothyroidism and proteinuria were reported as adverse events in 122 subjects (17.5%) and 117 subjects (16.7 %), respectively. Grade 3+ events occurred most frequently for hypertension (134 subjects, 19.2%), fatigue (90 subjects, 12.9%), and diarrhea (65 subjects, 9.3%).

Efficacy

Completed Single-Agent Axitinib Studies

Preliminary evidence of antitumor activity has been observed across multiple tumor types testing axitinib as a single agent. Response assessments for subjects with solid tumors were evaluated according to RECIST. Efficacy results for completed Phase 2 studies are summarized in **Table 5**.

Table 5: Efficacy of Axitinib in Completed Single-agent Phase 2 Clinical Studies [References [53-57]]

Protocol Number	Tumor Type	N	ORR (%)	mPFS/mTTP (months)	mOS (months)
A4061011	NSCLC (advanced)[a]	32	9	4.9	14.8
A4061012	mRCC (cytokine-refractory)[b]	52	44	15.7	29.9
A4061014	[^{131}]-I -refractory thyroid cancer[c]	60	38	15.1	35.6
A4061015	Melanoma (advanced)[d]	32	19	3.9	6.6
A4061023	mRCC (sorafenib-refractory)[e]	62	23	7.4	13.6
A4061035	mRCC (cytokine refractory- Japan only)	64	50[f]	11.0[f]	N/A

ORR: objective response rate; mOS: median overall survival; mPFS: median progression-free survival; mTTP: median time to progression; N: total number of subjects, N/A: not yet available

[a] Schiller JH et al, 2009
[b] Rixe O et al, 2007
[c] Locally advanced or metastatic (Cohen EE et al, 2008)
[d] No more than 1 prior systemic therapy (A4061015 Pfizer clinical study report, 2009)
[e] Failed at least 1 prior sorafenib-containing regimen (Rini BI et al, 2009)
[f] According to Independent Radiology Review committee (Tomita Y et al, 2011)

Table 6: Efficacy results from the Phase 3 study in previously-treated patients with advanced RCC comparing axitinib vs. sorafenib [58]

	Axitinib	Sorafenib	HR (95% CI)	P-value
Overall ITT	N= 361	N = 362		
Median PFS[a,b] in months (95% CI)	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)	0.67 (0.54, 0.81)	<0.0001[c]
Median OS in months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	0.3744
ORR % (95% CI)	19.4 (15.4, 23.9)	9.4 (6.6, 12.9)	2.06[d] (1.41, 3.00)	0.0001
PFS by prior treatment				
Sunitinib-refractory subgroup	N=194	N=195		
Median, months (95% CI)	4.8 (4.5, 6.4)	3.4 (2.8, 4.7)	0.74 (0.57, 0.96)	0.0107
Cytokine-refractory subgroup	N=126	N=125		
Median, months (95% CI)	12.1 (10.1, 13.9)	6.5 (6.3, 8.3)	0.46 (0.32, 0.68)	<0.0001

CI: Confidence interval; HR: Hazard ratio (axitinib/sorafenib); ITT: Intent to treat; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival

[a] Time from randomization to progression or death due to any cause, whichever occurs first.
[b] Assessed by independent radiology review according to RECIST.
[c] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy (comparison is considered statistically significant if the one-sided p-value is <0.023).
[d] Risk ratio is used for ORR. A risk ratio >1 indicated a higher likelihood of responding in the axitinib arm; a risk ratio <1 indicated a higher likelihood of responding in the sorafenib arm.

1.3 RATIONALE

The long-term survival for malignant PHEO/PGL may be limited because of its hormonal effects as well as its aggressive behavior and dissemination, particularly in some hereditary PHEO/PGL. Although several therapeutic modalities have been used to palliate malignant PHEO/PGL, a continued search for new agents to address the malignancy is needed to improve outcomes. One approach is to utilize drugs that target signaling pathways leading to decreased proliferation and survival of cancer cells. Some data in the literature suggests that in malignant PHEO/PGL, VEGF seems to play a role in the biology of the cancer and thus, its inhibition could reduce tumor growth. Sunitinib and imatinib has been used in a limited number of malignant pheochromocytomas with varying responses. Axitinib was designed to inhibit VEGFR that participates in tumor angiogenesis. In order to determine the activity of axitinib in tumor and hormonal responses in malignant PHEO/PGL, it will be used as a single agent in this study. The combination of cyclophosphamide; vincristine and dacarbazine have been shown to produce partial responses in malignant PHEO/PGL. The majority of the patients may have already received this combination or will receive this combination chemotherapy in the future. Our goal is to develop multiple lines of effective treatments for this disease.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

Adults with a confirmed pathologic diagnosis of pheochromocytoma/paraganglioma by the Laboratory of Pathology, NCI when such tissue is available to confirm
or
In the event that outside tissue is not available:

- an outside pathology report confirms the diagnosis of Pheo/PGL, AND
- the patient has nuclear medicine imaging studies that would only be positive in an adult patient with a diagnosis of Pheo/PGL (F-DOPA, Dotatate, F-Dopamine or MIBG)

2.1.1.1 Imaging confirmation of metastatic disease

2.1.1.2 Measurable disease at the time of enrollment per RECIST 1.1. See Section **6.3** for the evaluation of measurable disease.

2.1.1.3 A life expectancy of at least 3 months and ECOG performance status ≤ 2

2.1.1.4 Age $\geq$ 18 years. Because no dosing or adverse event data are currently available on the use of Axitinib in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

2.1.1.5 Information available or pending regarding possible genetic alterations that can explain the patient's pheochromocytoma/paraganglioma (mutations in SDHB, SDHV or VHL genes)

2.1.1.6 Last dose of chemotherapy or experimental therapy more than 4 weeks (6 weeks in the case of nitrosourea) prior to enrollment date; 2 weeks if the last therapy was received as part of a "phase 0" or "exploratory IND" trial. Last surgery more than 4 weeks prior to

enrollment, to allow for wound healing. Core biopsies or FNA will not require any waiting period

2.1.1.7 Last radiotherapy treatment ≥ 4 weeks prior to starting treatment with this protocol and there must be sites of measurable disease that did not receive radiation

2.1.1.8 Prior therapeutic MIBG is allowed

2.1.1.9 Organ and marrow function as defined below:

2.1.1.10 Total bilirubin ≤ 1.5 x ULN (upper limit of normal), unless the patient meets the criteria for Gilbert's Syndrome. The upper limit value for bilirubin for subjects with Gilbert's Syndrome is less than 3 mg/dl.

- Note: A diagnosis of Gilbert's disease will be made in the presence of (1) unconjugated hyperbilirubinemia noted on several occasions; (2) normal results from CBC count, reticulocyte count, and blood smear; (3) normal liver function test results; and (4) an absence of other disease processes that can explain the unconjugated hyperbilirubinemia.

2.1.1.11 AST ≤ 2.5 x ULN, ALT ≤ 2.5 x ULN

2.1.1.12 Amylase and lipase equal to, or less than, the institutional ULN.

2.1.1.13 Creatinine clearance ≥ 40 ml/min (estimated or measured creatinine clearance) or serum creatinine ≤ 1.6 mg/dl

2.1.1.14 Random urine protein < 20 mg/dL. If ≥ 20 mg/dL then a 24-hour urine protein collection will be performed to accurately demonstrate that the 24-hour total is <1000 mg, the level acceptable for enrollment on study

2.1.1.15 Absolute neutrophil count ≥ 500/mm^3

2.1.1.16 Platelet count ≥ 50,000/ mm^3

2.1.1.17 Ability to understand and sign an informed consent document.

2.1.1.18 Ability and willingness to follow the guidelines of the clinical protocol including visits to NICHD and NCI, Bethesda, Maryland for treatment and follow up visits.

2.1.1.19 Because the effects of chemotherapy on the developing human fetus are potentially harmful, women of childbearing potential and men who participate in the study must agree to use adequate contraception (hormonal or barrier methods) before, during the study and for a period of 3 months after the last dose of chemotherapy.

2.1.2 Exclusion Criteria

2.1.2.1 Patients with pheochromocytoma/paraganglioma tumors potentially curable by surgical excision alone as determined by the Principal Investigator in discussions with the surgical consultants.

2.1.2.2 Patients who have large abdominal masses impinging on bowel or pulmonary masses with encroached vessels and a potential to bleed will be considered on case by case basis after careful consultation with multiple disciplines such as radiologists and surgeons with main intent being patient safety.

2.1.2.3 Unstable hypertension defined as a systolic blood pressure >150 mm Hg or diastolic pressure > 90 mmHg despite optimal medical management.

2.1.2.4 Untreated brain metastases (or local treatment of brain metastases within the last 6 months) due to the poor prognosis of these patients and difficulty ascertaining the cause of neurologic adverse events.

2.1.2.5 Pregnancy, due to the possible adverse effects on the developing fetus.

2.1.2.6 Lactating women who are breast-feeding due to the possibility of transmitting axitinib to the child.

2.1.2.7 The presence of a second malignancy, other than squamous cell carcinoma of the skin or in situ cervical cancer because it will complicate the primary objective of the study. Cancer survivors who have been free of disease for at least one year can be enrolled in this study.

2.1.2.8 Patients with evidence of a bleeding diathesis

2.1.2.9 Patients must not have received prior therapy with a TKI. Prior TKI usage in pheochromocytoma affects the same pathway as axitinib.

2.1.2.10 Gastrointestinal abnormalities including:

- Inability to take oral medications
- Requirement for intravenous alimentation
- Prior surgical procedure affecting absorption including total gastric resection
- Treatment for active peptic ulcer disease in the past 6 months
- Active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy
- Malabsorption syndrome

2.1.2.11 Current use or anticipated need for treatment with drugs that are known potent CYP3A4 inhibitors (i.e., grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, telithromycin, clarithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, and delavirdine).

2.1.2.12 Current use or anticipated need for treatment with drugs that are known CYP3A4 or CYP1A2 inducers (i.e., carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, and St. John's wort).

2.1.2.13 Requirement of anticoagulant therapy with oral vitamin K antagonists. Low-dose anticoagulants for maintenance of patency of central venous access devices or prevention of deep venous thrombosis is allowed. Therapeutic use of low molecular weight heparin is allowed.

2.1.2.14 Active seizure disorder or evidence of brain metastases, spinal cord compression, or carcinomatous meningitis.

2.1.2.15 Any of the following within 12 months prior to study drug administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic

congestive heart failure, cerebrovascular accident or transient ischemic attack and within 6 months before study drug administration for deep vein thrombosis or pulmonary embolism.

2.1.2.16 Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study

2.2 SCREENING EVALUATION

2.2.1 History and Physical Evaluation

Focused history and physical examination (including height, weight, vital signs and ECOG performance score) with documentation of 1) measurable disease, 2) opioid use and pain assessment and 3) prior therapies (surgical, radiotherapeutic and cytotoxic) will be conducted prior to starting therapy.

2.2.2 Baseline Imaging Studies

Every patient should have a baseline clinical evaluation with CT scan of neck, chest, abdomen and pelvis prior to receiving treatment. In some patients an MRI may be more appropriate. Attempts will be made to obtain an FDG-PET scan prior to treatment in all patients, but this may be obtained after treatment starts. These must be completed within 28 days of enrollment.

2.2.3 Baseline EKG

- Should be obtained within 28 days prior to enrollment.

2.2.4 Baseline Laboratory Evaluation

To be obtained within one week prior to enrollment

- Hematological Profile: CBC with differential and platelet count, prothrombin time, activated partial thromboplastin time
- Biochemical Profile: electrolytes, BUN, creatinine, glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase, amylase and lipase
- Urine β-hCG for female patients of childbearing age who have not had prior gynecologic surgery that precludes the possibility to bear children
- Urine protein: A random urine will be obtained for protein. If the random urine protein level is ≥ 20 mg/dL then a 24-hour urine protein collection will be performed to accurately demonstrate that the 24-hour total is <1000 mg, the level acceptable for enrollment on study
- Hormonal profile: 24-hour urinary catecholamines and metanephrines; plasma catecholamines and metanephrines
- Thyroid Panel: TSH, Free T4, and T3
- Chromogranin A will be obtained in patients who are not taking antacids or H-2 blockers such as Zantac, Prilosec, Tums, or Pepsid. They should be off antacids and H-2 blockers for at least 2 weeks prior to blood test for reliable results. In patients who take these medications on a routine basis, the test will not be done.

2.2.5 Histologic confirmation of pheochromocytoma/paraganglioma when available **OR** review of outside pathology report and Nuclear Medicine imaging to confirm diagnosis.

NOTE: Stained slides, a block of primary tissue, or 10 unstained sections on charged slides from the time of diagnosis will be sought for each patient. If needed for confirmation of diagnosis these will be submitted to the Laboratory of Pathology/CCR to be used in confirmation of the diagnosis. Otherwise they may be used for research purposes. Tissue blocks from a known recurrence are an acceptable substitute if original tumor samples are unavailable

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with 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 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 to the research team. A recorder is available during non-working hours.

2.4 TREATMENT ASSIGNMENT PROCEDURES

Cohorts

Number	Name	Description
1	Cohort 1	Patients with pheochromocytoma/paraganglioma

Arms

Number	Name	Description
1	Arm 1	Axitinib 5 mg twice a day on a 28-day cycle

Randomization and Arm Assignment

Subjects in cohort 1 will be assigned to arm 1.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN [CYCLE LENGTH = 28 DAYS]

- In the first 16 weeks of therapy, patients will be seen in clinic every 4 weeks to monitor therapy. Occasionally exceptions will be made to allow for shorter or longer intervals to accommodate weather and personal circumstances. We will allow a 7-day flexibility plan when needed, although every effort will be made to stay on schedule.
- After the first 16 weeks patients will be seen every 12 weeks, with 7-days flexibility before or after the target date.
- A history and physical examination will be performed at each outpatient visit (for medical record only, not for research record)
- Every twelve weeks appropriate scans will be repeated as summarized in section **3.4**.

- Intrapatient dose escalations will be allowed beginning at week 4 for all patients who meet criteria (section **3.3**)
- CBC with differential, electrolyte panel, hepatic panel, mineral panel, urine analysis, serum amylase, and serum lipase every 4 weeks in the first sixteen weeks, and then at every re-assessment. A thyroid panel (TSH, free T4, and T3) will be obtained at baseline, every 4 weeks x 2, and then every 12 weeks (+/- 1 week)
- Conventional imaging studies deemed appropriate for monitoring the patient's disease as done for on-study disease assessment will be obtained and reviewed every 12 weeks. Measurable disease will be monitored as described in section **6.3**
- Hypertension can occur with axitinib. In the Investigator's Brochure, the frequency of hypertension adverse events was 42% including a 13% incidence of grade 3 hypertension. Therefore, all patients must have blood pressure measured and recorded twice daily during the first 4 weeks after starting therapy or after any dose escalation, then once daily or three times per week as needed and recorded in a patient diary. These diaries will be kept in a research record but the BID and/or daily or three times a week BP measurements will not be recorded in C3D. Patients and study team members will communicate by phone to discuss the blood pressure readings during the initial 4 weeks and at other times when daily monitoring is necessary. The guidelines for management of blood pressure elevation are in section **3.3.3**

3.2 DRUG ADMINISTRATION

3.2.1 Axitinib Administration

3.2.1.1 Patients will receive axitinib twice daily on a continuous dosing regimen and this will generally be administered on an outpatient basis except when admission is required for clinical reasons or research purposes. Reported adverse events and potential risks are described in Section **11.1.2**. Appropriate dose modifications for axitinib are described in Section **3.3**

3.2.1.2 Axitinib is supplied as 1- and 5-mg tablets and is administered orally twice a day with or without food. Patients are to swallow the tablets whole with approximately 250 ml of water, each morning and evening (i.e., every 12 hours)

3.2.1.3 Axitinib will be given as self-administered oral doses at the initial level of 5 mg every 12 hours continuously in a 28-day cycle. All patients will be evaluated for dose escalation beginning at week 4. In addition to the starting dose level of 5 mg every 12 hours, two additional levels (7 and 10 mg on every-12-hour schedules) will be considered. An interval of at least 4 weeks must elapse between any dose escalations. (See Section **3.3**)

3.2.2 Self-Administered Study Drugs

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from Pfizer Pharmaceuticals, Inc. Study drug acquisitions, inventory, and dispensing will be documented using the NIH Clinical Center Pharmacy Department's Investigational Drug Monitoring System. Axitinib, an oral self-administered investigational agent, will be accounted for, handled, and disposed of in accordance with CCR Policy # Clin-1, "Policy on Documenting, Handling and Disposing of Oral Investigational Agents that are Self-Administered by NCI CCR patients. The Standard Operating

Procedure # Clin-1, "Standard Operating Procedure for Conducting and Documenting Drug Accountability for Oral Investigational Agents that are Self Administered by Patients at the CCR" identifies activities associated with drug accountability and compliance monitoring for orally self administered investigational agents. Study drug will be dispensed in light-resistant containers. Each patient will be instructed to document in a study diary (**Appendix B**) the daily intake of axitinib, including the time the dose is taken and whether or not any doses are missed, BP self monitoring and to date and sign the entry. They will bring the study diary and any unused drug to their next scheduled clinic appointment. Clinic staff will (1) collect all "old" [i.e., empty bottle(s), partial bottle(s) or full bottle(s)] of study drug; (2) perform a capsule count and record the results on the approved CCR Pill Count Case Report Form which is to be maintained in the research record; and (3) dispense the new partial and full bottle(s) of axitinib to the patient. Unused study drugs are to be returned to the research nurse who will dispose of them according to the SOP.

3.3 Intrapatient Dose Escalation and Dose Modification for Toxicities

Subjects will be monitored closely for adverse events. In addition to optimizing supportive care as described in Section **4.2**, axitinib doses may be adjusted for individual subjects. The dose levels are found in **Table 7**.

Table 7: Axitinib dose levels

Starting dose level 1	5 mg every morning; 5 mg every evening
Dose level 2	7 mg every morning; 7 mg every evening
Dose level 3	10 mg every morning; 10 mg every evening
Dose level –1	3 mg every morning; 3 every evening
Dose level –2	2 mg every morning; 2 mg every evening

3.3.1 Intra-patient dose escalations

After four weeks of therapy, patients who tolerate axitinib for at least two consecutive weeks with no adverse reactions > Grade 2 (CTCAE V4), with the exception of hypertension, that will be limited to not > Grade 1, may have their dose increased. When a dose increase from 5 mg twice daily is recommended, the axitinib dose may be increased to 7 mg twice daily, and further to 10 mg twice daily using the same criteria. Dose escalations may not occur more frequently than every four weeks and should be in increments of one dose level. Patients are eligible for dose escalation whether or not they are receiving antihypertensive medication at the time of study entry.

3.3.2 Dose reductions

Dose reductions will be according to the guidelines in **Table 8**.

Table 8: Axitinib-related adverse events

Grade	Response
G1	Continue axitinib
All G2 except G2 PPES*	Maintain axitinib dose with symptomatic treatment
G2 PPES and all G3	Interrupt axitinib administration and re-evaluate at least weekly until

	the adverse event improves to ≤Grade 1 or to the pre-treatment baseline. The axitinib dose will be reduced one dose level (DL –1) the first time a grade 3 adverse event is recorded, and after resuming axitinib treatment, reduced a second dose level (DL –2) if the adverse event recurs and a further dose reduction is required. Grade 3 metabolic adverse events that can be corrected to ≤Grade 1 or to pre-treatment baseline within 48 hours will not necessitate a dose reduction. Patients who experience an adverse event ≥Grade 3 that does not resolve to ≤Grade 1 or baseline within 3 weeks will have treatment discontinued and be removed from study
G4	Discontinue therapy if a Grade 4 *clinical* adverse event is recorded. Grade 4 *metabolic* adverse events will be managed as Grade 3 adverse events.

*Abbreviations used PPES: palmar-plantar erythrodysesthesia syndrome

3.3.3 Management of Hypertension:

New or additional antihypertensive therapy should be started if 2 BP readings, preferably taken in the clinic and separated by at least 1 hour, show the following: 2 systolic BP readings greater than 150 mm Hg or 2 dBP readings greater than 100 mm Hg. Alternately, the dose of existing antihypertensive medication(s) may be increased. If the patient is already on maximal antihypertensive treatment, the axitinib dose should be reduced by 1 dose level Or the addition of Demser should be considered (see below).

Patients who have 2 systolic BP readings, separated by at least 1 hour, greater than 160 mm Hg, or 2 dBP readings, separated by at least 1 hour, greater than 105 mm Hg, should have treatment with axitinib held. (Note: if axitinib is held, patients receiving antihypertensive medications should monitor closely for hypotension and restart axitinib at one lower dose level as soon as BP is <150/100 mm Hg. Plasma half-life of axitinib is 2 – 4 hours and BP usually decreases within 1-2 days following dose interruption). Treatment with axitinib should be restarted at 1 lower dose level as soon as the systolic blood pressure reduces to less than 150 mm Hg and the dBP reduces to less than 100 mm Hg.

Patients who develop recurrent systolic hypertension (2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg) or recurrent diastolic BP >100 mm Hg following previous axitinib dose reduction should undergo another dose reduction by one dose level.

Guidance on dose interruption and reduction for hypertension is summarized in the **Table 9**, below.

Many patients with PHEO/PGL may have taken or may be taking Demser (metyrosine) to manage hypertension caused by malignant PHEO/PLG. This protocol allows the continued use of Demser while receiving axitinib if the patient has been Demser as part of their pre-study regimen.

If a patient begins axitinib as part of this study, and develops hypertension or has worsening hypertension, Demser can be considered as a possible option to control blood pressure when the standard antihypertensive medications have not been effective. In this case a treatment break

from axitinib may be needed in order to allow Demser dosing for 10-14 days prior to resuming axitinib.

Table 9: Hypertension Management Plan for Axitnib

Degree of Blood Pressure Elevation			Management
Systolic Pressure		Diastolic Pressure	• If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and maintain dose of axitinib • If on maximal antihypertensive treatment, reduce axitinib to one lower dose level • Interrupt dosing and begin Demser treatment for 10-14 days and then resume axitinib at the same dose level.
2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg	OR	2 BP readings separated by at least 1 hour show diastolic pressure >100 mm Hg	
2 BP readings separated by at least 1 hour show systolic pressure >160 mm Hg	OR	2 BP readings separated by at least 1 hour show diastolic pressure >105 mm Hg	• Interrupt dosing[A]; adjust antihypertensive medication; as soon as BP is less than 150/100 mm Hg, restart axitinib at one lower dose level. • Interrupt dosing and begin Demser treatment for 10-14 days and then resume axitinib at same dose level.
Recurrent hypertension following previous dose reduction (2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg)	OR	Recurrent dBP >100 mm Hg (2 BP readings separated by at least 1 hour) following previous dose reduction	Repeat axitinib dose reduction by one lower dose level. If a patient is on an axitinib dose of 2 mg every 12 hours, discontinue axitinib
G4 Hypertension			Discontinue axitinib

[A]If axitinib is held, patients receiving antihypertensive medications should monitor closely for hypotension. Plasma half-life of axitinib is 2 – 4 hours and BP usually decreases within 1-2 days following dose interruption

3.3.4 Management of Proteinuria:

- If a random urine protein level is ≥ 20 mg/dL, perform a 24-hour urine collection. Dosing may continue while waiting for test results.
- If < 2 g proteinuria/24 hour is reported, continue dosing at the same dose level.
- If ≥ 2 g proteinuria/24 hours is reported, hold dosing and repeat 24-hour urine collection for proteinuria and creatinine clearance (interval at investigator discretion) until proteinuria is < 2 g/24 hours. Restart axitinib at the same dose or one lower dose level at discretion of the investigator.

Note: The presence of hypertension and proteinuria favors the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), because angiotensin inhibitors restore nephrin expression. Calcium channel blockers may interact with anti-VEGF drugs through a cytochrome P-450 pathway, thus exposing patients to a risk of under-dosage or over-dosage of the anti VEGF agent. Newly enrolled subjects on calcium-channel blockers will be changed to alternative antihypertensive medications, with ACE-inhibitors as the first choice and ARB as an alternative. If calcium-channel blocker use is deemed necessary, it will be used only under approval of the PI.

Note: In case of hypertensive crisis (Grade 4 NCI CTCAE), axitinib will be discontinued.

3.4 STUDY CALENDAR

Baseline evaluations including laboratory examinations, and history and physical exam conducted within one week prior to administration of protocol therapy. Scans must be done within four weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

		Week																	
	Pre-Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Q 12 wk[e]	Off Study[k]
Axitinib[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent	X																		
Medical history, physical exam vital signs, PS	X					X				X				X				X	X
Concurrent medications	X	X ----------																	
Diary review						X				X				X				X	X
CBC[b], serum chemistry[b]	X	X				X				X				X				X	X
Plasma Catecholamines /metanephrines	X	X				X				X				X				X	X
24-hour urine catecholamines + metanephrines	X	X				X				X				X				X	X
Urinalysis (for protein, Protein Creatinine ratio)	X					X				X				X				X	X
PT/PTT	X	X								X								X	
TSH, Free T4, T3	X					X				X				X				X	X
Chromogranin A[f]	X								X								X	X	
EKG	X																		
Adverse event evaluation	X	X ----------																	X

		Week																	
	Pre-Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Q 12 wk[e]	Off Study[k]
Imaging[c] and tumor measurements	X									X								X	
Research blood sample[d]	X									X								X	
Advanced Directive [j]	X																		

[a]Axitinib will be taken twice daily for 28 days as one cycle

[b] BUN, creatinine, glucose, AST (SGPT), ALT (SGPT), bilirubin, calcium, phosphorous, magnesium, sodium, potassium, total protein, albumin, alkaline phosphatase, amylase, lipase, within one week prior study entry. CBC with differential & Platelet should also be obtained within one week prior to study entry

[c] CT scan of chest, abdomen and/or pelvis and FDG-PET scan examining areas of known or suspected disease involvement prior to receiving treatment. In some patients an MRI may be more appreciate. This must be completed within 28 days prior to enrollment. During therapy patients will undergo CT or MRI staging every 12 weeks (+/- 1 week).

[d] Research labs will be obtained at baseline, then at 8, 16 and 24 weeks. See section 5.1 for tube type and volume.

[e] After 16 weeks on study

[f] Chromogranin A will be obtained in patients who are not taking antacids or H-2 blockers such as Zantac, Prilosec, Tums, Pepsid, They should be off for at least 2 weeks prior to blood test for reliable results. In patients who take these medications on a routine basis, the test will not be done.

[j] As indicated in section **10.3**, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

[k] Off study visit: patients will be invited to clinical center approximately four weeks following the last dose of study drug. If patents are not able to come, they will be asked by phone for performance status, any adverse events and new cancer treatment.

3.5 SURGICAL GUIDELINES

If a major surgery or an interventional procedure (*e.g., endoscopy) is required, treatment with axitinib must be interrupted at least 36 – 48 hours before the procedure and the patient blood pressure should be closely monitored for hypotension. Patients may resume axitinib seven days after minor surgery and 2-3 weeks after major surgery, assuming their wound has completely healed and no wound healing complications (e.g., delayed healing, wound infection or fistula). Axitinib should be held for a minimum of 4 weeks in any patient undergoing elective bowel surgery.

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to documenting removal from study, effort must be made to have all subjects complete a safety visit approximately 4 weeks following the last dose of study therapy.

3.6.1 Criteria for removal from protocol therapy:

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression as defined in section **6.3.5**
- Intercurrent illness that prevents further safe administration of treatment
- Unacceptable adverse event(s) as described in section **3.3**
- Non-compliance to therapy regimen
- Patient decides to stop therapy
- Investigator discretion
- Positive pregnancy test

3.6.2 Off-Treatment Assessment

- Patients will be assessed approximately 4 weeks following the last dose of study drug with
    - Laboratory: Chemistries as defined in section **3.4**, CBC
    - Medical history and physical exam

[These assessments can be performed by the patient's local physician or at the NCI in Bethesda]

- Patients will be removed from study 4 weeks following off treatment date if assessment indicates they have met the criteria for disease progression. If they have not met disease progression criteria, they will remain on study in order to determine their Progression Free Survival (PFS). Follow-up will be provided via either clinic visits or phone calls until such time as the patient either has disease progression, or begins an alternative treatment. Once progression has been determined, they will be removed from study.

3.6.3 Off-Study Criteria

- Progression of disease and completion of off-study assessment
- Death
- Patient wishes to withdraw from the study
- Patient receives an alternative treatment

The reason for removal from study will be documented.

3.6.4 Off Protocol Therapy and Off-Study Procedure

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

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 CONCURRENT THERAPIES

- Incubation with recombinant CYP enzymes and human liver microsomes in the absence and presence of specific chemical inhibitors of human CYP suggest axitinib metabolism is

primarily mediated by CYP3A4/5, and to a lesser extent by CYP1A2, CYP2C19 and UGT1A1.

- All potent CYP3A4/5 inhibitors (ketoconazole, itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, indinavir, saquinavir, ritonavir, atazanavir, nelfinavir) are not permitted within 7 days before dosing with axitinib.
- The following CYP3A4/5 inducers (rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John's wort, efavirenz, tipranavir) are not permitted within 12 days before dosing with axitinib.
- During the study, potent CYP3A4/5 inhibitors and inducers are not recommended. Alternative therapies should be used when available. If usage of a potent CYP3A4 inhibitor or inducer is necessary, this must be in agreement with the Principal Investigator. See **Appendix A** for a complete list of CYP3A4/5 inhibitors, inducers and substrates.
- The use of coumarin derivative anticoagulants such as warfarin (Coumadin®) is not recommended, though warfarin doses up to 2 mg daily are permitted for prophylaxis of thrombosis
- Tobacco use will be strongly discouraged because smoking is a potent CYP1A2 inducer. Any subjects that are current smokers at the time of screening evaluation will be counseled regarding the interactions of smoking with the study medication and asked to cease smoking. If they are willing to stop or limit smoking they will be considered for eligibility and allowed to enroll if they meet other eligibility requirements
- The following antihypertensive medications commonly used in the treatment of pheochromocytoma are acceptable to use in conjunction with axitinib: phenoxybenzamine, propranolol and metyrosine.

4.2 SUPPORTIVE CARE

Patients will be allowed to use erythropoietin or erythropoietin analogs prior to entry and during the course of the study.

4.2.1 Hand-foot reaction

- Patients receiving axitinib who develop hand-foot reaction will be allowed to use topical emollients (e.g., Aquaphor® or Eucerin®), topical and/or oral steroids, antihistamine (H_1-receptor antagonist) agents, or vitamin B6 (pyridoxine: 50 to 150 mg orally each day).

4.2.2 Nausea/vomiting

- Patients will not be given primary antiemetic prophylaxis. If a patient develops nausea/vomiting, antiemetics will be instituted for treatment of this side effect and may receive secondary antiemetic prophylaxis during continuing treatment with axitinib. Axitinib has been characterized as presenting minimal-low emetic risk; therefore, NK_1 antagonists are not indicated and 5-HT_3 antagonists should not be needed unless adverse effects preclude use of other antiemetic options.

4.2.3 Diarrhea

- If diarrhea develops, and does not have an identifiable cause other than axitinib therapy, administer loperamide 4 mg p.o. after the first loose stool and 2 mg p.o. after each loose stool

thereafter The occurrence of liquid stools after a 24 h diarrhea-free period will be considered a new episode.

- If a patient develops blood or mucus in the stool, dehydration or hemodynamic instability, or if diarrhea persists > 48 h despite loperamide: discontinue loperamide and hospitalize the patient for treatment with IV fluids as needed.
- For persistent diarrhea, other potentially helpful treatments may also be administered, such as somatostatin analogues, propantheline bromide, tincture of opium, diphenoxylate+atropine (Lomotil®) etc. Note: Propantheline bromide is not on the Clinical Center's medication formulary and will not be readily available for dispensing from the Clinical Center pharmacy

4.2.4 Hypothyroidism

- Axitinib is known to cause hypothyroidism. Patients will receive replacement thyroid hormone according to standard medical practice if their thyroid function indicates hypothyroidism and is clinically indicated.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

As of amendment D all patients have completed the 24-week follow up and research samples are no longer being collected on this study.

5.1.1 Tissue Analysis for Potential Targets/Pathways Affected by Axitinib

Note on archival material: In order to accomplish these tests, a block of archival tumor material will be requested from each patient. A recent resection sample or blocks of tissue from the original resection will be requested. Where a block cannot be released by the governing Pathology Department, at least ten 10 x 8 mm re-cuts on charged slides will be requested.

5.1.1.1 Immunoblots/Immunohistochemistry:

The primary targets that may be evaluated based upon pre-clinical signaling data include but are not limited to the following: VEGFR-1, -2 and -3, AKT, p-AKT, ERK1/2, p-ERK1/2, MEK, p-MEK, IGF1R, pIGF1R. These tests will be performed in the Department of Pathology, or in Dr. Sherry Yang's laboratory BLDG 37, Rm 1048, phone 301-435-5409.

5.1.1.2 Studies of Microvessel Density

Microvessel staining may be done in the Department of Pathology, or in Dr. Sherry Yang's laboratory, but will not be required. Archival materials will be stained and analyzed for microvessel density (MVD) using standard immunohistochemical assays. Quantification of MVD will be performed using the method of Weidner et al. [59,60]. Section will be stained for CD31 expression. Sections will then be screened to determine the most vascular area of the tumor (hot spot). Within the hot spot area, the stained microvessels will be counted as a single high-power (x 400) field.

5.1.2 Enumeration of Circulating Endothelial Cells (CEC)

Early increase of CEC following anti-angiogenic drug administration can be an interesting marker of treatment efficacy. Interpretation of CEC change must take into account multiple factors such as the mechanism of drug action, time of CEC measurement to drug administration,

phenotype of CEC quantified [33,34]. Theoretically, various antigens can be used to characterize mature CEC. In general CD45 expression is used to exclude hematopoietic cells, CD133 to exclude immature cells. Commonly used endothelial markers include CD31, 146, 34, 144 or 105. However, there is a lack of consensus regarding combination to characterize CEC by flow cytometry analysis. In this study, we will evaluate pre- and post-treatment changes in mature circulating endothelial cells (CD 146+, CD133-), as determined by flow cytometry analysis. This evaluation will be conducted in Jane Trepel's lab, NIH/NCI/GMB.

5.1.2.1 Specimen Collection

Blood samples should be drawn in 3 Blue/Black CPT tubes for a total volume of 24mLs at baseline and then weeks 8, 16 and 24.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.2.1 Samples Managed by Dr. Fojo's Laboratory

5.2.1.1 Storage/Tracking

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

Research samples will be obtained from patients, as described in the protocol. Patient samples will either be processed and assayed fresh or will be coded in the laboratory of Dr. William Figg and then stored in a Liquid Nitrogen freezer in the laboratory of Dr. Tito Fojo. Records of sample acquisition will be held in the laboratory in a computerized database that is accessible by password. A limited number of laboratory staff will have access to identifying patient information.

5.2.1.2 Protocol Completion/Sample Destruction:

Material remaining after completion of correlative studies will be transferred to the laboratory of Dr. William Figg. These samples will be managed in accordance with the laboratory's policies and procedures. Any new use of the samples, specimens, or data will require prospective IRB review and approval.

5.2.2 Samples Managed by Dr. Figg's Laboratory

5.2.2.1 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center

patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.2.2.2 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

5.2.3 Protocol Completion/Sample Destruction:

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NCI IRB as soon as he is made aware of such loss. If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for 30 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Data will not be distributed outside NIH without IRB notification.

Dr. Fojo will continue to have access to the data for purposes of data analysis and publication when he is at Columbia University. He will have access to the data via a secure flash drive. It is also possible that data will be sent to him via encrypted email.

6.1.1 Exceptions for Data Recording

Data Recording during Long-term follow-up: When a subject has entered long-term follow-up only a limited amount of information will be recorded in C3D:

- Progression-free survival and survival status, determined via phone calls, submission of imaging studies or actual clinic visits
- Imaging Response per section **6.3.5**

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share de-identified human data generated in this research for future research as follows:

- De-identified data in a NIH-funded or approved public repository: clinicaltrials.gov
- De-identified data in BTRIS
- De-identified in publication and/or public presentations

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository: clinicaltrials.gov.
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- At the time of publication or shortly thereafter.

6.3 RESPONSE CRITERIA

6.3.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks (+/- 1 week). In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [61]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.2 Definitions

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

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

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

6.3.3 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:

- By chest x-ray: $\geq$20 mm;
- By CT scan:
    - Scan slice thickness 5 mm or under as $\geq$10 mm with CT scan
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: $\geq$10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

6.3.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical

examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

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

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

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

6.3.5 Evaluation of Target Lesions

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

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

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

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

6.3.6 Evaluation of Non-Target Lesions

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

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

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

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

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

6.3.7 Evaluation of Biochemical Response

Complete Biochemical Response (CR-B) – all major markers used for evaluation such as plasma or urinary catecholamines or metanephrines have normalized

Partial Biochemical Response (PR-B) – at least a 50% decrease, but not normalization, of the markers

Progressive Disease (PD-B) – at least a 25% increase of any major biochemical marker

Stable Disease (SD-B) – all other courses not described above.

6.3.8 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)					
Target Lesions	Non-Target Lesions	New Lesions	Biochemical	Overall Response	Best Overall Response when Confirmation is Required[A]
CR	CR	No	CR-B	CR	≥4 wks. Confirmation[B]
CR	Non-CR/ Non-PD	No	CR-B, PR-B, or SD-B	PR	≥4 wks. Confirmation[B]
CR	Not evaluated	No	CR-B, PR-B, or SD-B	PR	
PR	Non-CR/	No	CR-B, PR-B,	PR	

For Patients with Measurable Disease (i.e., Target Disease)					
Target Lesions	Non-Target Lesions	New Lesions	Biochemical	Overall Response	Best Overall Response when Confirmation is Required[A]
	Non-PD/ Not evaluated		or SD-B		
PR	Non-CR/ Non-PD/ Not evaluated	No	CR-B, PR-B, or SD-B	PR	
SD	Non-CR/ Non-PD/ Not evaluated	No	SD-B	SD	Documented at least once ≥4 weeks from baseline[B]
PD	Any	Yes or No	Any	PD	No prior SD, PR or CR
Any	PD[C]	Yes or No	Any	PD	
Any	Any	Yes	Any	PD	
Any	Any	Yes or No	PD-B	PD	

[A]See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
[B]Only for non-randomized trials with response as primary endpoint.
[C]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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)		
Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[A]
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

[A]'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease; to assign this category when no lesions can be measured is not advised

6.3.9 Duration of Response

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

recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

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

6.3.10 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

6.3.11 Response Review

At the conclusion of the study, all responses will be reviewed by an expert(s) independent of the study. Simultaneous review of the patients' files and radiological images is the planned approach.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or,

if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

(a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

(b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

7.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and the NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.3 IND SPONSOR REPORTING CRITERIA

An investigator must **immediately** report to the sponsor, using the mandatory MedWatch form 3500a, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. For serious adverse events that occur more

than 30 days after the last administration of investigational agent/intervention, only report those that have an attribution of at least possibly related to the agent/intervention.

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

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7.4 Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.4.2 Sponsor Monitoring Plan

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

8 STATISTICAL CONSIDERATIONS

8.1 SELECTION BASED ON GENDER, ETHNIC BACKGROUND, OR RACE

Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. No information suggests that there are differences in drug metabolism or disease response in any patient subgroup based on gender, race, or ethnic background. Efforts will be made to accrue a representative population and if differences in outcome are noted to correlate with gender, race, or ethnicity, accrual may be expanded or a follow-up study written to investigate these differences.

8.2 JUSTIFICATION FOR EXCLUSIONS

Due to lack of knowledge of the effects of axitinib on the fetus or on infants, as well as the possibility of teratogenic effects, pregnant and nursing women will be excluded from this trial. Patients with HIV on protease inhibitors are excluded because information on drug interactions of anti-HIV agents with axitinib are lacking. Patients with unstable or serious medical conditions (ongoing or active infection, symptomatic congestive heart failure (AHA Class II or worse), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements) are excluded due to the possibility that axitinib may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events with respect to axitinib. Patients under the age of 18 will be excluded from study. The effect of axitinib in children may be investigated in studies that exclusively enroll children.

8.3 STUDY DESIGN/ENDPOINTS

The primary objective of this study is to conduct a Phase II trial to determine if axitinib is able to be associated with sufficient clinical responses to merit further consideration for use in patients with metastatic pheochromocytoma/paraganglioma.

Secondary objectives are to determine the progression-free survival and to explore the relationship of potential biological markers of axitinib activity with clinical outcomes. Specifically, to examine the extent of activation of the VEGFR pathway in pheochromocytoma/paraganglioma in a qualitative manner by immunoblot and in a semi-quantitative manner by immunohistochemistry staining; and also to assess the effect of axitinib on the VEGFR pathway for patients who have repeat biopsies taken while on treatment.

The study will be conducted using a phase II optimal design [62]. The objective of the trial will be to determine if axitinib is able to be associated with a response rate (PR + CR), which can rule out 5% (that is, p 0 = 0.05) in favor of a more desirable 20% response rate (p1 = 0.20). Using alpha = 0.10 (probability of accepting a poor drug) and beta = 0.10 (probability of rejecting a good drug), initially 12 patients will be enrolled onto the trial. If zero of the 12 patients respond, then accrual will end, and we will conclude that the agent is unable to demonstrate a response

rate that is worthy of further consideration in this population. If 1 or more of 12 patients have a CR or PR, then accrual will continue until a total of 37 patients with measurable disease have been enrolled. If 1-3 of these 37 have a CR or PR, this will be considered inadequate for further investigation, while if 4 or more of 37 have a response, this will warrant further investigation in a subsequent trial. Under the null hypothesis (5% response rate), the probability of early termination is 54%. Primary clinical responses (PR + CR) will be assessed at 12 weeks (+/- 1 week). If zero of 11 patients responded, accrual will stop up to 4 months waiting to evaluate the last patient's response before continuing accrual.

8.4 SAMPLE SIZE/ACCRUAL RATE

The accrual ceiling to the trial will be set at 37 patients. It is expected that 1 - 3 patients per month will enroll onto this protocol. Thus, accrual is expected to complete within 2-3 years. We receive approximately 2 referrals from Dr. Karel Pacak in NICHD each month. Many of these will be eligible for this study. If we are unable to enroll 8 patients in the first year, accrual will be stopped.

8.5 ANALYSIS OF SECONDARY ENDPOINTS

Exploratory non-parametric analyses using trend tests will be performed to describe the relationship between the translational endpoints and the clinical outcome, primarily. Since all of these analyses will be performed with exploratory intent, the analysis results will be presented without any adjustment for multiple comparisons, but with careful discussion of the hypothesis-generating nature of the analyses undertaken. Analysis for statistically significant correlations will be planned for the following parameters defined as being of particular interest but are not limited to the following: VEGFR-1, -2 and -3, AKT, p-AKT, ERK1/2, p-ERK1/2, MEK, p-MEK, IGF1R, pIGF1R. and Microvessel Density (CD31 staining)

In general, it is anticipated that non-parametric analyses will generally be used for these evaluations because of the limited number of subjects. In view of the exploratory nature of these analyses, any p-values reported will not be adjusted for multiple comparisons, and results of any such analyses will be stated carefully as being hypothesis generating, requiring additional confirmation.

For all evaluable patients (subjects who received at least 2 cycles), Kaplan-Meier analyses of progression free survival will also be performed. Appropriate confidence intervals at selected time points will also be provided. Since these will be considered secondary endpoints. The results will be reported as part of the descriptive report of the study.

Adverse events will be tabulated by type and grade, for all types of adverse events identified as being at least possibly attributable to the agent.

9 COLLABORATIVE AGREEMENTS

9.1 AGREEMENT TYPE

Axitinib is an investigational agent supplied to investigators by the Pfizer Pharmaceuticals, Inc. Axitinib is provided to NCI under a Clinical Trial Agreement (CTA).

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

This study will be open to all individuals with pheochromocytoma/paraganglioma regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. This study will be recruited through internal referral, our local physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). It should be noted that for the past several years we have seen on average over 80 new referrals per year. Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in section 2. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or 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, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

10.2 PARTICIPATION OF CHILDREN

Patients under the age of 18 will be excluded from study. The effect of axitinib in children may be investigated in studies that exclusively enroll children.

10.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.4**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH 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.

10.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The potential benefit to a patient who enters study is a reduction in the bulk of his/her tumor, which may or may not have a favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects that are listed in the pharmaceutical section and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described earlier.

10.5 RISKS/BENEFITS ANALYSIS

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at NIH's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

10.6 CONSENT PROCESS AND DOCUMENTATION

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, treatment 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 of the signed informed consent will be placed in the patient's medical record and a copy in the research record. 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.

10.6.1 Reconsent via the telephone

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator.

10.6.2 Informed consent of non-English speaking subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2), and 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

11 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

11.1 AXITINIB 109,131

11.1.1 Source

Axitinib is an investigational agent supplied to investigators by the Pfizer Pharmaceuticals, Inc. Axitinib is provided to the NCI under a CTA (see section **9.1**).

11.1.2 Toxicity

The most commonly reported treatment-related adverse events of severity Grade 3 or higher were hypertension (39 subjects, 14%), fatigue (27 subjects, 10%), diarrhea (12 subjects, 4%), palmar plantar erythrodysaesthesia syndrome (8 subjects, 3%), hypertension aggravated (5 subjects, 2%), and stomatitis (5 subjects, 2%), elevated triglycerides (1 subject, < 1%).

Table 10: Treatment-Emergent, All-Causality Adverse Events in at Least 10% of Subjects with Solid Tumors Receiving Single Agent Axitinib

MedDRA Preferred Term	Solid Tumor Single-Agent (N = 268)[a]		AML/MDS Single-Agent (N = 12)		Total (N = 280)	
	All Grades n (%)	Grade 3+ n (%)	All Grades n (%)	Grade 3+ n (%)	All Grades n (%)	Grade 3+ n (%)
Fatigue	167 (62.3)	36 (13.4)	7 (58.3)	0	174 (62.1)	36 (12.9)
Diarrhea	112 (41.8)	15 (5.6)	10 (83.3)	1 (8.3)	122 (43.6)	16 (5.7)
Hypertension	113 (42.2)	35 (13.1)	5 (41.7)	4 (33.3)	118 (42.1)	39 (13.9)
Nausea	106 (39.55)	4 (1.5)	6 (50.0)	0	112 (40)	4 (1.4)
Anorexia	98 (35.6)	6 (2.2)	2 (16.7)	0	100 (35.7)	6 (2.1)
Dysphonia[b]	69 (25.8)	0	9 (75.0)	0	78 (27.9)	0
Dyspnea	73 (25.7)	17 (6.3)	4 (33.3)	1 (8.3)	77 (27.5)	18 (6.4)
Weight decreased	71 (26.5)	5 (1.9)	2 (16.7)	0	73 (26.1)	5 (1.8)
Arthralgia	69 (25.8)	9 (3.4)	0	0	69 (24.6)	9 (3.2)
Constipation	65 (24.2)	1 (0.4)	2 (16.7)	0	67 (23.9)	1 (0.4)
Headache	62 (23.1)	9 (3.4)	3 (25.0)	0	65 (23.2)	9 (3.2)
Vomiting	60 (22.4)	4 (1.5)	3 (25.0)	0	63 (22.5)	4 (1.4)
Cough	55 (20.5)	5 (1.9)	5 (41.7)	0	60 (21.4)	5 (1.8)
Pain in extremity	54 (20.2)	5 (1.9)	0	0	54 (19.3)	5 (1.8)
Dyspepsia	51 (19)	1 (0.4)	0	0	51 (18.2)	1 (0.4)
Mucosal inflammation	37 (13.9)	1 (0.4)	4 (33.3)	1 (8.3)	41 (14.6)	2 (0.7)
Stomatitis	37 (13.8)	7 (2.6)	4 (33.3)	0	41 (14.6)	7 (2.5)
Abdominal pain	35 (13.1)	8 (3.0)	2 (16.7)	1 (8.3)	37 (13.2)	9 (3.2)
Back pain	33 (12.3)	4 (1.5)	3 (25.0)	0	36 (12.9)	4 (1.4)
Insomnia	35 (13)	1 (0.4)	3 (25.0)	0	38 (13.6)	1 (0.4)
Peripheral edema	32 (12)	0	1 (8.3)	0	33 (11.8)	0
Rash	29 (10.8)	1 (0.4)	4 (33.3)	0	33 (11.8)	1 (0.4)
Dizziness	31 (11.2)	1 (0.4)	2 (16.7)	0	33 (11.8)	1 (0.4)
Dry Skin	31 (11.6)	0	1 (8.3)	0	32 (11.4)	0
Myalgia	29 (10.9)	3 (1.1)	0	0	29 (10.4)	3 (1.1)
Palmar plantar erythrodysaesthesia syndrome	28 (10.5)	8 (3.0)	0	0	28 (10)	8 (2.9)

*Includes Protocols A4060010, A4061008, A4061011, A4061012, A4061013, A4061014, A4061015, A4061023. Studies A4061022 and A4061027 are not included. See Table 38 for actual cutoff dates for various studies treating subjects with single agent AG-013736.

AML/MDS = acute myeloid leukemia/mylodysplastic syndrome

[a] Includes 8 patients enrolled in continued access Protocol A4061008.

[b] Includes adverse events reported as hoarseness.

Table 11: Laboratory Test Results Reported for Subjects with Solid Tumors Receiving Single-Agent Axitinib.

Group/Parameter[b]	Std Units	N	n (%)[a] at Maximum Grade				
			Grade 1	Grade 2	Grade 3	Grade 4	Total
Chemistry							
Alkaline Phosphatase	U/L	201	62 (30.8)	13 (6.5)	3 (1.5)	0	78 (38.8)
Bicarbonate	mEq/L	71	18 (25.4)	1 (1.4)	0	0	19 (26.8)
Creatinine	mg/dL	196	44 (22.4)	8 (4.1)	1 (0.5)	8 (4.1)	61 (31.1)
Hypoalbuminemia	g/dL	201	49 (24.4)	17 (8.5)	1 (0.5)		67 (33.3)
Hypercalcemia	mg/dL	86	13 (15.1)	0	1 (1.2)	1 (1.2)	15 (17.4)
Hypocalcemia	mg/dL	86	8 (9.3)	0	0	2 (2.3)	10 (11.6)
Hyperglycemia	mg/dL	199	86 (43.2)	17 (8.5)	11 (5.5)	0	114 (57.3)
Hypoglycemia	mg/dL	199	28 (14.1)	3 (1.5)	0	2 (1.0)	33 (16.6)
Hyperkalemia	mEq/L	201	42 (20.9)	10 (5.0)	2 (1.0)	0	54 (26.9)
Hypokalemia	mEq/L	201	27 (13.4)	0	1 (0.5)	0	28 (13.9)
Hypermagnesemia	mg/dL	38	8 (21.1)	0	1 (2.6)	0	9 (23.7)
Hypomagnesemia	mg/dL	38	12 (31.6)	0	0	0	12 (31.6)
Hypernatremia	mEq/L	201	8 (4.0)	0	0	0	8 (4.0)
Hyponatremia	mEq/L	201	41 (20.4)	0	7 (3.5)	2 (1.0)	50 (24.9)
SGOT (AST)	U/L	201	50 (24.9)	7 (3.5)	8 (4.0)	0	65 (32.3)
SGPT (ALT)	U/L	201	45 (22.4)	9 (4.5)	7 (3.5)	0	61 (30.3)
Total Bilirubin	mg/dL	201	16 (8.0)	10 (5.0)	3 (1.5)	0	29 (14.4)
Hematology							
Hemoglobin	g/dL	197	61 (31.0)	12 (6.1)	0	3 (1.5)	76 (38.6)
Platelets	$10^3/mm^3$	197	25 (12.7)	1 (0.5)	2 (1.0)	0	28 (14.2)
White Blood Cells	$10^3/mm^3$	197	13 (6.6)	3 (1.5)	0	1 (0.5)	17 (8.6)
Neutrophils (Abs)	$10^3/mm^3$	131	12 (9.9)	3 (2.3)	0	1 (0.8)	15 (11.5)
Lymphocytes (Abs)	$10^3/mm^3$	163	28 (17.2)	17 (10.4)	16 (9.8)	15 (9.2)	76 (46.6)
Urinalysis							
Urine Protein	QUAL	239	32 (13.4)	34 (14.2)	2 (0.8)	0	68 (28.5)

Thirty-five (35) of 280 subjects (13%) treated with single agent axitinib discontinued therapy because of treatment-related adverse events (see **Table 10**).

Table 12: Treatment-Related Averse Events Resulting in Treatment Discontinuation for Subjects Receiving Single Agent Axitinib at 5 mg twice daily

Event	No. of Subjects, n (%) (N = 27)
Any treatment-related event leading to withdrawal	*27(100)*
Hypertension	5 (19)
Fatigue	4 (15)
Intestinal perforation	2 (7)
Stomatitis	2 (7)
Cerebral hemorrhage	2 (7)
Abdominal pain (lower)	1 (4)
Anorexia	1 (4)
Aphasia	1 (4)
Bone pain	1 (4)
Bradycardia	1 (4)
Cardiomyopathy	1 (4)
Cerebrovascular accident	1 (4)
Diarrhea NOS	1 (4)
Dyspnea	1 (4)
Gout	1 (4)
Headache	1 (4)
Hemoptysis	1 (4)
Hypotension	1 (4)
Hypothermia	1 (4)
Medical device discomfort	1 (4)
Myocardial infarction	1 (4)
Myocardial ischemia	1 (4)
Nausea	1 (4)
Proteinuria	1 (4)
Thrombosis	1 (4)
Wound complication	1 (4)

Note: Axitinib 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.

11.1.3 Formulation and preparation

Axitinib is supplied as an immediate-release film-coated tablets containing either 5 mg or 1 mg of the free base, axitinib, and common compendial excipients. The 5 mg tablets are red and triangular; the 1 mg tablet is red and oval. The film coating has no effect on the rate of release of the active axitinib.

11.1.4 Stability and Storage

Store at controlled room temperature storage within the temperature range 20° – 25°C (68° – 77°F) with excursions permitted to 15° - 30° C (59° – 86°F). Storage conditions should not exceed 25ºC. The current shelf life is 24 months when stored at controlled room temperature.

11.1.5 Administration procedures

Oral, axitinib should be taken with at least 250 mL of water and will be given with or without food.

11.1.6 Incompatibilities

11.1.6.1 Product Description

Axitinib is white to light yellow crystalline powder.

Chemical Name: N-Methyl-2-[3-((E)-2-pyridin-2-yl-vinyl-)-1H-indazol-6-ylsulfanyl]-benzamide

Other Names: AG-013736

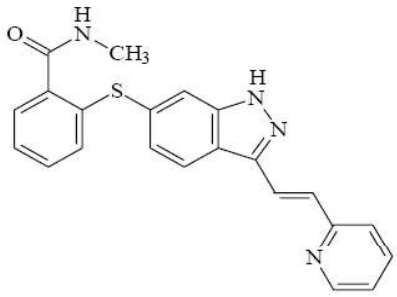
Classification: Kinase inhibitor (VEGF-R, and PDGF-R)

Mechanism of Action: Axitinib (AG-013736) is an oral, potent and selective inhibitor of VEGF receptors 1, 2, 3 (vascular endothelial growth factor receptors 1, 2, 3). Preclinical data suggest that axitinib has anti-tumour activity that appears to result from its anti-angiogenic activity, which is reversible when treatment is discontinued

Molecular Formula: $C_{22}H_{18}N_4OS$

Molecular Weight: 386.47 Daltons

Structural formula:



11.1.6.2 Drug Interactions

Incubation with recombinant CYP enzymes and human liver microsomes in the absence and presence of specific chemical inhibitors of human CYP suggest axitinib metabolism is primarily mediated by CYP3A4/5, and to a lesser extent by CYP1A2, CYP2C19 and UGT1A1. A mean 2-fold ***increase*** in exposure of axitinib was observed when axitinib was co-administered with ketoconazole, a potent inhibitor of CYP3A4/5. A mean 3.5-fold ***decrease*** in axitinib plasma exposure was observed when axitinib was co-administered with rifampin, a potent inducer of CYP3A4/5. Therefore, co-administration with potent inhibitors (ketoconazole, itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, indinavir, saquinavir, ritonavir, atazanavir, nelfinavir) and inducers (rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John's wort, efavirenz, tipranavir) of CYP3A4/5 may result in significant increases and decreases in exposure of axitinib, respectively, and may alter the safety/efficacy of the drug. All potent CYP3A4/5 inhibitors and inducers are not permitted within 7 and 12 days, respectively, before commencing axitinib administration. During the study, potent CYP3A4/5 inhibitors and inducers are not recommended in concurrent use with axitinib. Alternative therapies should be used when available. If usage of a potent CYP3A4/5 inhibitor or inducer is necessary, this must be in agreement with the Sponsor. The use of coumarin derivative

anticoagulants such as warfarin (Coumadin®) is not recommended, though warfarin doses up to 2 mg daily are permitted for prophylaxis of thrombosis.

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13 APPENDICES

13.1 APPENDIX A: LIST OF DRUGS THAT MAY HAVE POTENTIAL CYP3A4 INTERACTIONS

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912. Only major substrates and effective inducers are listed. Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/

CYP3A4 Substrates

Albuterol	Dihydroergotamine	Isradipine	Quinidine
Alfentanil	Diltiazem	Itraconazole	Rabeprazole
Alprazolam	Disopyramide	Ketamine	Ranolazine
Amiodarone	Docetaxel	Ketoconazole	Repaglinide
Amlodipine	Doxepin	Lansoprazole	Rifabutin
Amprenavir	Doxorubicin	Letrozole	Ritonavir
Aprepitant	Doxycycline	Levonorgestrel	Salmeterol
Aripiprazole	Efavirenz	Lidocaine	Saquinavir
Atazanavir	Eletriptan	Losartan	Sibutramine
Atorvastatin	Enalapril	Lovastatin	Sildenafil
Benzphetamine	Eplerenone	Medroxyprogesterone	Simvastatin
Bisoprolol	Ergoloid mesylate	Mefloquine	Sirolimus
Bortezomib	Ergonovine	Mestranol	Spiramycin
Bosentan	Ergotamine	Methadone	Sufentanil
Bromazepam	Erythromycin	Methylergonovine	Sunitinib
Bromocriptine	Escitalopram	Methysergide	Tacrolimus
Budesonide	Estradiol	Miconazole	Tamoxifen
Buprenorphine	Estrogens, conj., synthetic	Midazolam	Tamsulosin
Buspirone	Estrogens, conj., equine	Miglustat	Telithromycin
Busulfan	Estrogens, conj., esterified	Mirtazapine	Teniposide
Carbamazepine	Estrone	Modafinil	Tetracycline
Cerivastatin	Estropipate	Montelukast	Theophylline
Chlordiazepoxide	Ethinyl estradiol	Moricizine	Tiagabine
Chloroquine	Ethosuximide	Nateglinide	Ticlopidine
Chlorpheniramine	Etoposide	Nefazodone	Tipranavir
Cilostazol	Exemestane	Nelfinavir	Tolterodine
Cisapride	Felbamate	Nevirapine	Toremifene
Citalopram	Felodipine	Nicardipine	Trazodone
Clarithromycin	Fentanyl	Nifedipine	Triazolam
Clobazam	Flurazepam	Nimodipine	Trimethoprim
Clonazepam	Flutamide	Nisoldipine	Trimipramine
Clorazepate	Fluticasone	Norethindrone	Troleandomycin
Cocaine	Fosamprenavir	Norgestrel	Vardenafil
Colchicine	Gefitinib	Ondansetron	Venlafaxine
Conivaptan	Haloperidol	Paclitaxel	Verapamil

Cyclophosphamide	Ifosfamide	Pergolide	Vinblastine
Cyclosporine	Imatinib	Phencyclidine	Vincristine
Dantrolene	Indinavir	Pimozide	Vinorelbine
Dapsone	Irinotecan	Pipotiazine	Zolpidem
Dasatinib (1)	Isosorbide	Primaquine	Zonisamide
Delavirdine	Isosorbide dinitrate	Progesterone	Zopiclone
Diazepam	Isosorbide mononitrate	Quetiapine	

Note: When drugs classified as 'substrates' are co-administered with *Axitinib*, there is the potential for higher concentrations of the 'substrate'.

CYP3A4 Inhibitors

Acetaminophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan	Progesterone
Amiodarone	Diltiazem	Lovastatin	Propofol
Amlodipine	Disulfram	Mefloquine	Propoxyphene
Amprenavir	Docetaxel	Mestranol	Quinidine
Anastrozole	Doxorubicin	Methadone	Quinine
Aprepitant	Doxycycline	Methimazole	Quinupristin
Atazanavir	Drospirenone	Methoxsalen	Rabeprazole
Atorvastatin	Efavirenz	Methylprednisolone	Ranolazine
Azelastine	Enoxacin	Metronidazole	Risperidone
Azithromycin	Entacapone	Miconazole	Ritonavir
Betamethasone	Ergotamine	Midazolam	Saquinavir
Bortezomib	Erythromycin	Mifepristone	Selegiline
Bromocriptine	Ethinyl estradiol	Mirtazapine	Sertraline
Caffeine	Etoposide	Mitoxantrone	Sildenafil
Cerivastatin	Felodipine	Modafinil	Sirolimus
Chloramphenicol	Fentanyl	Nefazodone	Sulconazole
Chlorzoxazone	Fluconazole	Nelfinavir	Tacrolimus
Cimetidine	Fluoxetine	Nevirapine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nicardipine	Telithromycin
Cisapride	Fluvoxamine	Nifedipine	Teniposide
Clarithromycin	Fosamprenavir	Nisoldipine	Testosterone
Clemastine	Glyburide	Nizatidine	Tetracycline
Clofazimine	Grapefruit juice (2)	Norfloxacin	Ticlopidine
Clotrimazole	Haloperidol	Olanzapine	Tranylcypromine
Clozapine	Hydralazine	Omeprazole	Trazodone
Cocaine	Ifosfamide	Orphenadrine	Troleandomycin
Conivaptan	Imatinib	Oxybutynin	Valproic acid
Cyclophosphamide	Indinavir	Paroxetine	Venlafaxine
Cyclosporine	Irbesartan	Pentamidine	Verapamil
Danazol	Isoniazid	Pergolide	Vinblastine
Dasatinib (1)	Isradipine	Phencyclidine	Vincristine
Delavirdine	Itraconazole	Pilocarpine	Vinorelbine
Desipramine	Ketoconazole	Pimozide	Voriconazole

Dexmedetomidine	Lansoprazole	Pravastatin	Zafirlukast
Diazepam	Lidocaine	Prednisolone	Ziprasidone

Note: When *Axitinib* is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of *Axitinib* is the potential outcome.

CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's wort (3)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

Note: The co-administration of 'inducers' would potentially lower plasma *Axitinib* concentrations.

Investigator's Brochure: Dasatinib (BMS 354825). Bristol-Myers Squibb. October 2006
Malhotra *et al*. (2001). Clin Pharmacol Ther. 69:14-23.
Mathijssen *et al*. (2002). J Natl Cancer Inst. 94:1247-1249
Frye *et al*. (2004). Clin Pharmacol Ther. 76:323-329.
Updated on May 1, 2007

13.2 APPENDIX B: STUDY DIARY

Day / Date	Axitinib taken yes/no	Blood Pressure: record your BP prior to taking axitinib. If >150/>100, repeat in 5 minutes. If still >150/>100, do not take axitinib and repeat in one hour. If <150/<100 take the axitinib; If still >150/>100 after one hour do not take the axitinib for that dose.	Symptoms, other medicines taken
Sunday Date:	AM Y/N time ___ PM Y/N time ___	AM BP _____, time_____ AM BP _____, time_____ if needed AM BP _____, time_____ if needed PM BP _____, time_____ PM BP _____, time_____ if needed PM BP _____, time_____ if needed	
Monday Date:	AM Y/N time ___ PM Y/N time ___	AM BP _____, time_____ AM BP _____, time_____ if needed AM BP _____, time_____ if needed PM BP _____, time_____ PM BP _____, time_____ if needed PM BP _____, time_____ if needed	
Tuesday Date:	AM Y/N time ___ PM Y/N time ___	AM BP _____, time_____ AM BP _____, time_____ if needed AM BP _____, time_____ if needed PM BP _____, time_____ PM BP _____, time_____ if needed PM BP _____, time_____ if needed	
Wednesday Date:	AM Y/N time ___ PM Y/N time ___	AM BP _____, time_____ AM BP _____, time_____ if needed AM BP _____, time_____ if needed PM BP _____, time_____ PM BP _____, time_____ if needed PM BP _____, time_____ if needed	
Thursday Date:	AM Y/N time ___ PM Y/N time ___	AM BP _____, time_____ AM BP _____, time_____ if needed AM BP _____, time_____ if needed PM BP _____, time_____ PM BP _____, time_____ if needed PM BP _____, time_____ if needed	
Friday Date:	AM Y/N time ___ PM Y/N time ___	AM BP _____, time_____ AM BP _____, time_____ if needed AM BP _____, time_____ if needed PM BP _____, time_____ PM BP _____, time_____ if needed PM BP _____, time_____ if needed	
Saturday Date	AM Y/N time ___ PM Y/N time ___	AM BP _____, time_____ AM BP _____, time_____ if needed AM BP _____, time_____ if needed PM BP _____, time_____ PM BP _____, time_____ if needed PM BP _____, time_____ if needed	

13.3 APPENDIX C: PFIZER FAX COVER FORM

On following page

Investigator-Initiated Research
Reportable Event Fax Cover Sheet

Use this fax cover sheet to fax a Reportable Event for Investigator-Initiated Research studies.

Include with this form the completed Pfizer Investigator-Initiated Research Serious Adverse Event (IIR SAE) form, MedWatch Form FDA 3500A-Mandatory Reporting, which can be obtained from the FDA website: www.fda.gov/medwatch/getforms.htm, or other Pfizer agreed-upon form for SAE reporting.

If you are using the MedWatch Form to report, the following information should be included in block 5 of the Adverse Events section:

- **The complete clinical course of the patient receiving Pfizer drug**
- **The causality assessment for each Reportable Event**
- **The action taken for each study drug and for each Reportable Event**
- **The outcome for each Reportable Event**

This cover sheet MUST be provided with each completed SAE form. Do not substitute forms/reports or submit additional documentation other than what is required.

Do not fax these forms to any additional fax numbers other than the one listed below.

TO:	*Pfizer U.S. Clinical Trial Department*	
FAX:	*1-866-997-8322*	
FROM: Maureen Edgerly, RN		DATE:
TELEPHONE: 301-435-5604		FAX: 301-402-1608
NUMBER OF PAGES (INCLUDING COVER SHEET):		
PRODUCT	Axitinib	
PFIZER REFERENCE NUMBER		EXTERNAL REFERENCE NUMBER
STUDY TITLE	*PHASE II STUDY OF AXITINIB (AG-013736) WITH EVALUATION OF THE VEGF-PATHWAY IN METASTATIC, RECURRENT OR PRIMARY UNRESECTABLE PHEOCHROMOCYTOMA CARCINOMA*	
PATIENT NUMBER		
INVESTIGATOR	Antonio Tito Fojo, MD, PhD	