Phase II Study Evaluating the Role of Pazopanib in Angiosarcoma

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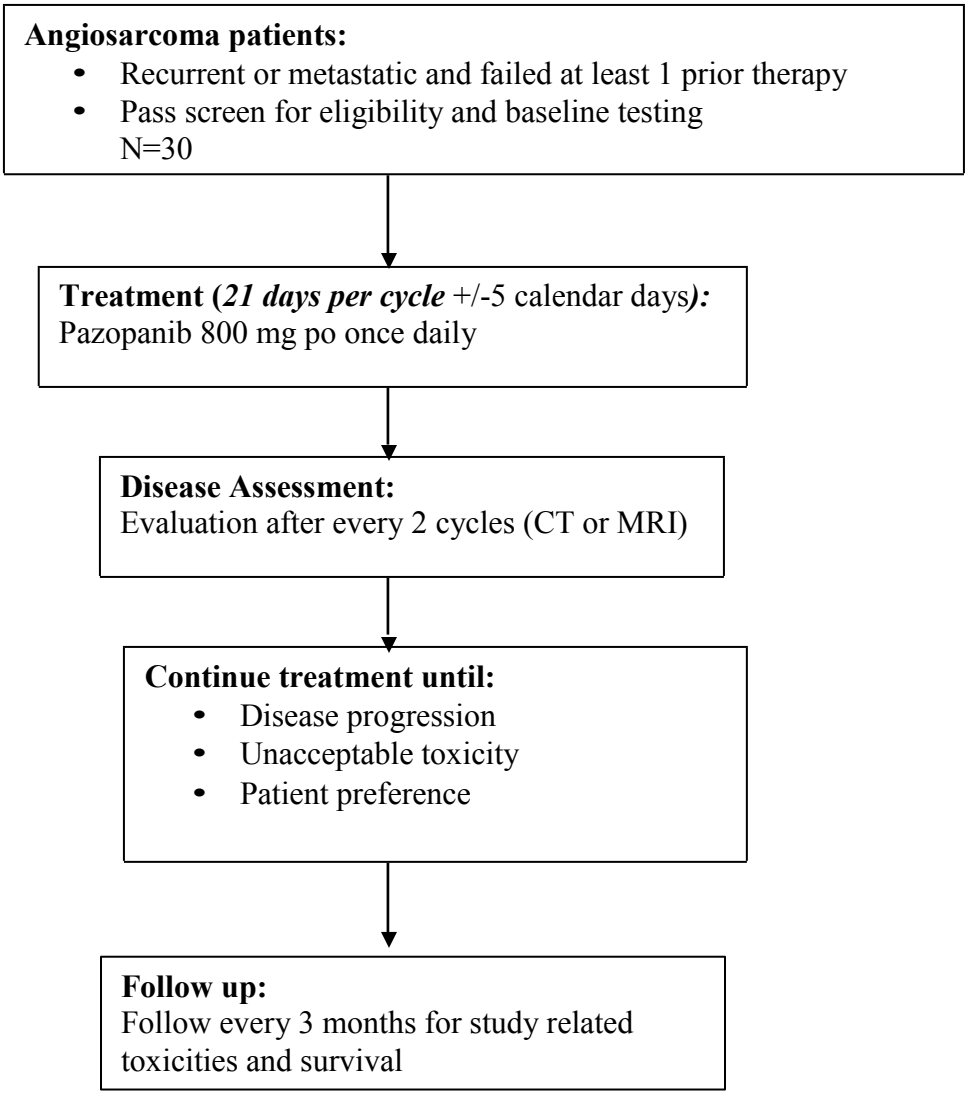

Primary objective: dual end points: RR and PFS at 3 months

Secondary Objective: endpoints: Median OS and toxicity

Table of Contents

1.1 Introduction

1.2 Angiosarcoma

Soft tissue sarcomas account for ~1% of adult malignancies. Angiosarcomas account for a small proportion of this 1% and arise from endothelial cells [1]. Angiosarcomas are most commonly seen on the face and scalp of elderly males. They have also been described in the setting of chronic lymphedema and post-radiation.[2], [3]. Data from the US Surveillance, Epidemiology and End Results registries from 1973-1997 reported 263 subsequent cases of sarcoma in 274,572 patients with breast cancer [4]. The cumulative incidence at 15 years post breast cancer diagnosis was 3.2 per 1,000 for those who received radiation therapy and 2.3 per 1,000 for those who did not receive radiation therapy (p=0.001). Overall 5-year survival was poor at 27-35%, however there was no difference in survival between those who did and did not receive radiation.

Therapy is primarily surgical, however these tumors have a propensity for recurrence and metastasis requiring eventual systemic therapy. Few systemic therapy options exist and response rates to existing agents are poor. Additionally, given the rarity of angiosarcomas, studies in sarcomas have included only very small numbers of patients with the angiosarcoma subtype. Most studies have evaluated doxorubicin based regimens with response rates ranging from 17% to 34%.[5-8]. The collective experience of physicians at Memorial Sloan Kettering Cancer Center reported a response in 8 out of 9 patients treated with paclitaxel either weekly or every three weeks for angiosarcomas of the scalp and face [9]. Given the frequent incorporation of radiation in the adjuvant treatment of breast cancer, the increasing incidence of breast cancer, we may see more of these tumors arising from blood vessels in the future. It is therefore prudent to evaluate newer possible therapies. Evaluation of paclitaxel in patients with metastatic angiosarcoma lead to a 74 and 45% PFS at 2 and 4 months respectively [10].

Preclinical studies in angiosarcoma tumor models have shown antitumor effects of antiangiogenic agents. Primate vascular endothelial growth factor 121 (VEGF121) was expressed in an endothelial cell line. Expression of VEGF121 resulted in slow growing endothelial tumor with histology similar to that seen in angiosarcoma. The endothelial cells were then treated with VEGFR-2 tyrosine kinase inhibitor SU-1498, which resulted in reduced expression of transcription factor ets-1, which is stimulated by VEGF [11]. Clinical studies evaluating agents with anti-angiogenic properties, such as sorafenib and bevacizumab have shown encouraging single agent activity in this disease [12], [13].

1.2 Study Drug - Pazopanib

Numerous growth factors and cytokines are involved in the angiogenic process, i.e., the process of new blood vessel formation, important in the development and progression of malignancy. Among these factors, VEGF has a predominant role

as a central mediator of tumor-related angiogenesis, and its expression has been shown to be an adverse prognostic factor for a number of solid tumors [14-16].

Pazopanib, being developed by GlaxoSmithKline (GSK) for the treatment of a variety of cancers, is a multi-target, small molecule inhibitor. It is an orally-bioavailable, ATP-competitive tyrosine kinase inhibitor of VEGF receptor (VEGFR) (-1, -2, and -3), platelet-derived growth factor receptor PDGFR (-α and -β)□, and c-Kit [17].

Clinical data from more than 20 clinical Phase I, II, and III studies are presented in the current version of the Investigator's Brochure (IB) (RR2002/00017/10). As of 09 September 2010, over 5000 subjects have been enrolled in pazopanib oncology clinical studies conducted by GSK or National Cancer Institute (NCI). Clinical data indicate that (a) pazopanib is absorbed after oral administration, (b) the 800 mg daily dosing regimen is an active monotherapy dose for subjects with cancer, providing optimal biologic and clinical effects associated with VEGFR inhibition, (c) pazopanib is generally well-tolerated at the 800 mg daily dosing regimen, and (d) pazopanib has encouraging efficacy in specific tumor settings such as Renal Cell Carcinoma (RCC), sarcoma, Non-Small Cell Lung Cancer (NSCLC), cervical and ovarian cancer.

The most common adverse events (AEs) reported for pazopanib monotherapy to date are diarrhea, fatigue, nausea, hypertension, hair color changes (hair depigmentation), anorexia, vomiting, dysgeusia, headache, abdominal pain, rash, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increases, constipation, cough, and arthralgia. Most of these events were Grade 1 or 2 using the National Cancer Institute-Common Toxicity Criteria of Adverse Events, Version 3.0 (NCI-CTCAE v3.0). The most frequent Grade 3 or 4 events were hypertension, fatigue, diarrhea, and AST and ALT increases. Less common AEs of note include hand-foot syndrome, mucositis/stomatitis, proteinuria, venous thrombotic events, and bleeding. Intestinal perforations and arterial thromboses were uncommon.

A review of serious adverse events (SAEs) across oncology studies revealed that the most frequently reported SAEs (≥ 50 events), regardless of causality and treatment regimen, as of 09 September 2010 in decreasing order of frequency were ALT increased, vomiting, dyspnea, abdominal pain, diarrhea, dehydration, pyrexia, fatigue, pneumonia, anemia, AST increased, nausea, pleural effusion, hypertension, and pulmonary embolism. A number of these events are known class effects of VEGF inhibitors.

1.2.1 Safety in clinical studies with monotherapy pazopanib

1.2.1.1 Subjects with RCC

Completed Study VEG105192: A Randomized, Double-blind, Placebo-controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of Pazopanib (GW786034) Compared to

Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma

A total of 435 subjects were enrolled in completed Study VEG105192 between 18 April 2006 and 24 April 2007. Two hundred and ninety subjects were randomized to the pazopanib arm and 145 subjects were randomized to the placebo arm [18].

As of the cut-off date of 23 May 2008, the median exposure time in the pazopanib arm was 7.4 months, almost twice the 3.8 months exposure in the placebo arm. The overall incidence of AEs reported during the study was higher in the pazopanib arm (92%) as compared with placebo (74%) (Table 1.1)

Most AEs were of Grade 1 or 2 intensity. More Grade 3 AEs were reported for the pazopanib arm (33%) compared with the placebo arm (14%). Grade 4 AEs were reported in 7% of subjects in the pazopanib arm and 6% in the placebo arm. The most frequent Grade 3 AEs in the pazopanib arm were ALT increased, AST increased, hypertension, and diarrhea. The rates for Grade 4 and Grade 5 events were similar between the pazopanib and placebo arms: Grade 4 AEs in 7% versus 6% and Grade 5 in 4% versus 3% respectively.

Table 1.1 Adverse Events Reported for at Least 10% of Subjects (Safety Population) in Study VEG105192

Preferred Term	Number (% of subjects)					
	Placebo (n=145)			Pazopanib (n=290)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE[a]	107 (74)	21 (14)	8 (6)	268 (92)	96 (33)	20 (7)
Diarrhea	13 (9)	1 (<1)	0	150 (52)	9 (3)	2 (<1)
Hypertension	15 (10)	1 (<1)	0	115 (40)	13 (4)	0
Hair color changes	4 (3)	0	0	109 (38)	1 (<1)	0
Nausea	13 (9)	0	0	74 (26)	2 (<1)	0
Anorexia	14 (10)	1 (<1)	0	65 (22)	6 (2)	0
Vomiting	11 (8)	3 (2)	0	61 (21)	6 (2)	1 (<1)
Fatigue	11 (8)	2 (1)	2 (1)	55 (19)	7 (2)	0
ALT increased	5 (3)	1 (<1)	0	53 (18)	18 (6)	3 (1)
AST increase	5 (3)	0	0	43 (15)	13 (4)	1 (<1)
Asthenia	12 (8)[b]	0	0	41 (14)	8 (3)	0
Abdominal pain	2 (1)	0	0	32 (11)	6 (2)	0
Headache	7 (5)	0	0	30 (10)	0	0

AEs are ranked by incidence in the pazopanib arm. Any AE, any grade includes Grade 5 (fatal) events (12 [4%] subjects in the pazopanib arm and 4 [3%] subjects in the placebo arm).

One placebo subject had Grade 5 asthenia.

AEs leading to permanent discontinuation of investigational product (IP) were reported for 44 (15%) subjects in the pazopanib arm and 8 (6%) subjects in the placebo arm, respectively. In the pazopanib arm, AEs associated with liver function/enzyme abnormalities (including increased ALT, AST, hepatotoxicity, increased hepatic enzyme, and hyperbilirubinemia) led to discontinuation of IP for 11 (3.8%) subjects while diarrhea led to discontinuation of IP for 6 (2%) subjects. For 3 of the 44 subjects in the pazopanib arm with AEs leading to discontinuation of IP, the investigator indicated that the reason for discontinuation was "other" since the investigator considered that disease progression also contributed to discontinuation of IP.

1.2.1.1.2 Laboratory abnormalities

The incidences of leukopenia, neutropenia, and thrombocytopenia with any grade increase relative to baseline were 37%, 34%, and 32%, respectively in the pazopanib arm, which were higher than those in the placebo arm (6%, 6% and 5%, respectively) (Table 1.2).

The incidences of grade increases in other hematologic parameters (i.e., lymphocytopenia, anemia, increased PTT, INR) were similar in the pazopanib and placebo arms.

Post-baseline increases to Grade 3 or Grade 4 in any hematologic parameter were uncommon in both treatment arms, occurring between <1% to 4%.

Table 1.2 Summary of Worst-case Hematologic Toxicity Grade Shift from Baseline (Safety Population) in Study VEG105192

Hematologic Toxicity	Number (%) of subjects							
	Placebo (n=145)				Pazopanib (n=290)			
	N	Any grade[a]	Grade 3	Grade 4	N	Any grade[a]	Grade 3	Grade 4
Leukopenia	144	9 (6)	0	0	280	103 (37)	0	0
Neutropenia	144	9 (6)	0	0	280	94 (34)	3 (1)	1 (<1)
Thrombocytopenia	144	7 (5)	0	1 (<1)	280	89 (32)	2 (<1)	1 (<1)
Lymphocytopenia	144	34 (24)	2 (1)	0	280	86 (31)	11 (4)	1 (<1)
Increased PTT	140	34 (24)	1 (<1)	0	271	72 (27)	4 (1)	0
Anemia	144	44 (31)	2 (1)	1 (<1)	280	62 (22)	5 (2)	2 (<1)
INR	128	25 (20)	2 (2)	0	246	42 (17)	4 (2)	0

PTT= Partial thromboplastin time; INR= International Normalized ratio.

a. Any grade increase from baseline. Subjects with missing baseline grade were assumed to have baseline grade of 0.

The most common increases relative to baseline in any toxicity grade for clinical chemistry parameters in the pazopanib arm were elevations in ALT, AST, and total bilirubin, which occurred in 53%, 53% and 36% subjects, respectively, compared with lower incidences in the placebo arm (22%, 19%, and 10% respectively) (Table 1.3). Other clinical chemistry parameters with a higher incidence in any grade increase in the pazopanib arm compared with the placebo arm included hypophosphatemia (34% versus 11%), hypoglycemia (17% versus 3%), hypokalemia (9% versus 2%), and hypomagnesemia (26% versus 14%). Although 17% of subjects in the pazopanib arm had any grade increase in hypoglycemia, only 1 subject had an increase above Grade 2.

ALT and AST elevation and hypophosphatemia were the most common clinical chemistry parameters with increases to Grade 3 (10%, 7% and 4%, respectively) in the pazopanib arm compared with lower rates in the placebo arm (1%, <1% and 0%, respectively). A toxicity grade

increase of clinical chemistry parameters to Grade 4 was uncommon (2% or less for any individual laboratory test) for both pazopanib and placebo arms.

Table 1.3 Summary of Worst-Case Toxicity Grade Shift from Baseline for Clinical Chemistry Parameters (Safety Population) in Study VEG105192

Clinical Chemistry Parameter	Number (%) of subjects							
	Placebo (n=145)				Pazopanib (n=290)			
	N	Any grade[a]	Grade 3	Grade 4	N	Any grade[a]	Grade 3	Grade 4
ALT increase	144	32 (22)	2 (1)	0	289	152 (53)	30 (10)	5 (2)
AST increase	144	27 (19)	1 (<1)	0	288	152 (53)	21 (7)	2 (<1)
Hyperglycemia	144	47 (33)	2 (1)	0	280	115 (41)	2 (<1)	0
Total Bilirubin increase	144	15 (10)	2 (1)	1 (<1)	280	102 (36)	7 (3)	2 (<1)
Hyponatremia	144	35 (24)	6 (4)	0	280	86 (31)	11 (4)	4 (1)
Hypophosphatemia	141	16 (11)	0	0	276	95 (34)	11 (4)	0
Hypocalcemia	137	35 (26)	2 (1)	1 (<1)	272	91 (33)	4 (1)	4 (1)
Hyperkalemia	144	33 (23)	7 (5)	0	280	76 (27)	12 (4)	1 (<1)
Alkaline phosphatase	144	50 (35)	3 (2)	0	280	75 (27)	4 (1)	1 (<1)
Creatinine increase	144	36 (25)	1 (<1)	0	280	73 (26)	0	2 (<1)
Hypomagnesemia	141	20 (14)	0	0	276	72 (26)	2 (<1)	4 (1)
Hypoglycemia	144	4 (3)	0	0	280	47 (17)	0	1 (<1)
Hypermagnesemia	141	13 (9)	3 (2)	0	276	31 (11)	9 (3)	0
Hypernatremia	144	11 (8)	0	0	280	30 (11)	2 (<1)	0
Hypercalcemia	137	25 (18)	2 (1)	0	272	29 (11)	0	4 (1)
Hypokalemia	144	3 (2)	0	0	280	24 (9)	3 (1)	2 (<1)

a: Any grade increase from baseline.

There was an apparent increase from baseline in the urine protein level (based on dipstick testing) in the pazopanib arm compared with the placebo arm.

1.2.1.1.3 Overall safety summary -Integrated data from Studies VEG105192, VEG102616, and VEG107769

The safety profile of pazopanib used in the treatment of RCC has been further defined in an integrated analysis of data from 593 subjects who received pazopanib across 3 RCC studies as of 09 January 2009. The database supporting the safety profile of pazopanib in subjects with RCC includes the completed placebo-controlled Phase III study VEG105192, with 290 subjects treated with pazopanib, a completed supportive Phase II study

(VEG102616) in which 225 subjects were treated with pazopanib, and the ongoing open-label extension study VEG107769 (n=78).

For the RCC studies described, the AE profile and hematology and laboratory chemistry abnormalities were similar to those seen for VEG105192 alone. As of 09 January 2009, the most common AEs reported in subjects receiving pazopanib included diarrhea (55%), hypertension (41%), hair color changes (40%), nausea (32%), fatigue (29%), anorexia (24%), vomiting (21%), and ALT increased (17%). Most of these events were Grade 1 or 2 using the NCI CTCAE Version 3.0. Commonly reported AEs with the most frequent Grade 3 classification were hypertension (6%), ALT increased (5%), and AST increased (4%). Grade 4 and Grade 5 events were infrequently reported (9% and 4%, respectively).

The most common chemistry abnormalities included ALT, AST, and bilirubin elevations, hyperglycemia and hypophosphatemia. Hyperglycemia was not significantly different in the pazopanib (41%) versus placebo (33%) arm of VEG105192 study, as of 23 May 2008, suggesting that hyperglycemia was unlikely to be drug induced. Most of these chemistry abnormalities were Grade 1/2. The most common Grade 3/4 laboratory abnormalities were ALT and AST elevations. Although leukopenia, neutropenia, and thrombocytopenia were not uncommon, Grade 3/4 cytopenias were generally uncommon as demonstrated in VEG105192 as of 23 May 2008.

The only significant urinalysis abnormality reported across the 3 RCC studies as of 23 May 2008 was proteinuria: 44 subjects (8%) reported an AE of proteinuria. Of those cases, most were Grades 1 or 2, but 5 subjects (<1%) had Grade 3 proteinuria and 1 subject had Grade 4 proteinuria.

Rare but severe AEs previously described for VEGFR inhibitors, such as cardiac/cerebral ischemia, hemorrhage, and bowel perforation, were observed with pazopanib treatment.

Across RCC studies as of 09 January 2009, 92 (16%) pazopanib-treated subjects experienced AEs leading to discontinuation or withdrawal from study. The most common AE leading to discontinuation from IP was an

increase in ALT (11 subjects, 2%). The next most common AEs leading to discontinuation were diarrhea, AST increased, and proteinuria (all 1% incidence).

In summary, pazopanib treatment in subjects with RCC was generally well tolerated with an AE profile similar to other VEGFR inhibitors. Most AEs were mild to moderate in severity and were reversible upon interruption or discontinuation of pazopanib.

1.2.1.1.4 Hepatotoxicity

Liver enzyme abnormalities were noted early in pazopanib clinical development and have been extensively evaluated. Close monitoring of liver markers (ALT, AST, bilirubin, and alkaline phosphatase) with strict stopping criteria was implemented in pazopanib protocols. While approximately half of all subjects who receive pazopanib experience some elevations in transaminases, few subjects (4%) had increases to ≥ 10xULN as of 09 January 2009. In addition, 1% subjects had concurrent ALT and bilirubin elevations, without significant alkaline phosphatase elevations, that might be predictive of possible development of hepatic functional impairment. Elevations in transaminases typically occurred in the first 18 weeks of treatment. Hepatobiliary adverse events that were not laboratory abnormalities were less common and liver failure and fatal hepatic events were rare. Three fatal hepatic events occurred: one in a subject for which an independent pathology review demonstrated massive hepatic replacement by tumor, a second in a subject with rapid disease progression in the liver (adjudicated as unrelated to study drug by an independent hepatologist), and a third in a subject with underlying cirrhosis who developed a fatal esophageal hemorrhage (independent hepatologist could not rule out contribution of study drug in the setting of underlying cirrhosis).

Across the RCC database (N=593), 107 (18%) subjects had an elevation in ALT ≥ 3xULN as of 09 January 2009. ALT is a more specific indicator of hepatocellular injury than AST and was therefore used as a single criterion for evaluating outcomes. Liver enzyme elevations were reversible upon cessation of the drug and in some cases while continuing on pazopanib. In an analysis performed across the RCC database, 96/106 (91%) subjects had full recovery. Recovery was defined as any ALT < 2.5xULN

after the first elevation including post-therapy tests. Seven of the remaining 10 subjects had limited or no follow-up to determine recovery and 3 died of cancer progression with no follow-up ALT data. It was noted early in development that some of the subjects with elevated hepatic enzymes remained on study drug despite these elevations and had normalization of their transaminases while remaining on pazopanib ("adaptation"). Most subjects with transaminase elevations in whom dosing was interrupted could be successfully re-challenged.

For purposes of this analysis, adaptation was defined as an ALT ≥ 3xULN while exposed to study drug followed by a return to grade 0 or baseline grade without any interruption of study drug. Subjects were considered to have been re-challenged if they developed ALT ≥ 3xULN during exposure to study drug which recovered to Grade 1 or below following interruption and subsequently received study drug at either the same or reduced dose. These subjects were evaluated for recurrence of ALT abnormalities following the re-challenge.

Adaptation:

- 32 subjects remained on study drug despite elevations of ALT ≥ 3xULN and experienced adaptation;
- 29 (91%) without dose reduction
- 3 (9%) after a dose reduction
- Median time to adaptation was 57 days (range 19-188 days)

Re-challenge:

- 31 subjects who had a dose interruption following an ALT elevation to ≥ 3xULN were re-challenged; 4 (13%) at the same dose and 27 (87%) at a lower dose. The dose was reduced from 800 mg to 400 mg in 24 subjects and from 400 mg to 200 mg in 3 subjects.
- Median duration of interruption prior to re-challenge was 19 days (range 5-139 days).
- The median duration of re-treatment among all re-challenge subjects was 194 days (range 2-681 days). The maximum ALT before re-challenge and the latest ALT prior to interruption did not appear to correlate with the likelihood of recurrent elevations.

- 20 (65%) subjects did not experience an ALT ≥ 3x ULN following a resumption of study drug;
- 10 (32%) subjects had recurrent elevations
- 2/10 (20%) subjects with recurrent elevations were continued on study drug and subsequently met the criteria for adaptation as defined above. Thus, these 2 subjects are counted both as re-challenges and as adaptations.
- 6/10 (60%) positive re-challenges recovered;
- 2/10 (20%) had inadequate follow-up to assess recovery.
- 1 (3%) subject had no follow-up data on the outcome of the re-challenge.

The remaining 45 subjects with increases in ALT ≥ 3xULN included 10 subjects with inadequate or absent follow-up data to assess recovery as well as those whose transaminases did recover either while remaining on pazopanib (but who did not meet criteria for adaptation and/or re-challenge) or after discontinuation of pazopanib.

1.2.1.1.5 Hypertension

The cumulative incidence of hypertension across the 3 primary RCC studies was similar to that of the pazopanib-treated subjects in the VEG105192 study. Two hundred and seventy-two (47%) out of 586 subjects experienced an on-study episode of hypertension (defined as systolic blood pressure of ≥ 150 mmHg and/or diastolic blood pressure of ≥ 100 mmHg). These subjects did not have hypertension at baseline. By Week 18, it was noted that 239 of these 272 subjects had at least 1 episode of hypertension, which was 87.9% of all occurrences of hypertension. By Week 24, it was noted that 249 of 272 subjects had at least 1 occurrence of hypertension, which was 91.5% of all episodes of hypertension that occurred on pazopanib during the RCC trials.

Only 6% of the RCC pazopanib-treated subjects reported Grade 3 hypertension. Most subjects had a maximum grade of 1-2 for these events. No Grade 4 or 5 hypertension event was reported in the RCC studies, with the exception of the Grade 4 SAE of hypertensive crisis.

1.2.1.1.6 Cardiac and vascular events

Cardiac and vascular events were categorized as follows: non-vascular cardiac events included arrhythmias and cardiac dysfunction while vascular events included arterial thrombotic events (myocardial infarction/ischemia, cerebral vascular accident and transient ischemic attack [TIA]) and venous thrombotic events (deep vein thrombosis, pulmonary embolus).

In VEG105192, the overall incidence rate of cardiac and vascular events was higher in the pazopanib arm compared with placebo (10% versus 6%). A comprehensive analysis of exposure-adjusted incidence rates of cardiac and vascular events (a rate of '10 per 100 patient-years' indicates that in a cohort of 100 patients each treated for 1 year, 10 patients would be expected to experience the event of interest) demonstrates a similar incidence across placebo and pazopanib in VEG105192 and in the integrated RCC.

While the exposure-adjusted incidence rates for all cardiac and vascular events were similar between the 2 arms (11.99 [CI 7.55, 16.43] per 100 patient-years in the pazopanib arm compared with 10.22 [CI, 3.14, 17.30] in the placebo arm), the exposure-adjusted incidence rate for Grade 5 events was higher on placebo (1.28 versus 2.55 per 100 patient-years). Analysis of exposure adjusted incidence rates of arrhythmia, cardiac dysfunction (cardiomyopathy), and venous thrombotic events demonstrate were similar between the placebo and pazopanib arm of study VEG105192 and the integrated the RCC population. The exposure adjusted incidence rate of arterial thrombotic events was higher in the pazopanib arm of VEG105192 compared with placebo (3.85 [CI 1.33, 6.37] versus 0 [CI could not be estimated] per 100 patient years). Subjects who experienced these events had underlying risk factors for arterial thrombotic events including male gender, age > 65, hypertension, tobacco use, diabetes and peripheral vascular disease (PVD).

Overall for the RCC program, QT prolongation (> 500 msec) occurred in 10/558 (1.8%) subjects treated with pazopanib. Two Torsades de Pointes cases have been identified. [Section 5.2.8.3 of the IB [RR2002/00017/10]].

1.2.1.1.7 Hemorrhagic events

Exposure-adjusted hemorrhagic event rates were higher on the pazopanib arm of VEG105192 compared with placebo, but similar to those seen in the integrated RCC population. The exposure-adjusted incidence rate was 15.95 (CI 10.74, 20.96) per 100 patient-years in the pazopanib arm compared to 8.94 (CI 2.32, 15.56) in the placebo arm. Hemoptysis/pulmonary hemorrhages and GI tract hemorrhages were the most common SAEs reported. Association to known metastases was noted for 4 of the 5 hemoptysis/pulmonary hemorrhagic SAEs and 3 of the 7 GI tract hemorrhagic SAEs. The most common hemorrhagic event was epistaxis. Life-threatening and fatal hemorrhagic events were uncommon across both the RCC and monotherapy populations.

1.2.1.1.8 Thyroid function abnormalities

Increases in thyroid stimulating hormone (TSH) are commonly noted in RCC subjects receiving pazopanib (29%). Most of these subjects do not appear to develop clinically overt hypothyroidism. Clinical hypothyroidism manifested as elevated T4 was noted in 6% of subjects. The hypothyroidism AE incidence rate was also low (4-7%) and similar between VEG105192 and across the RCC studies for pazopanib-treated subjects.

Hyperthyroidism occurs infrequently (1%) and the incidence was not significantly different in subjects receiving pazopanib compared to those receiving placebo on study VEG105192.

1.2.1.1.9 Bowel Perforations and Enteral Fistulae

In the RCC population, 5 subjects (0.9%) suffered SAEs related to GI perforations or fistulae. The 5 events were described as follows: ileal perforation (n=1), large intestine perforation (n=2), peritonitis secondary to intestinal perforation (n=1), and enterocutaneous fistula (n=1). Two of these events, large intestine perforation and peritonitis secondary to intestinal perforation were fatal. One event of large intestinal perforation was associated with diverticulitis. Three events of perforation were related to underlying tumor.

1.2.1.10 Amylase and Lipase elevations

In VEG102616, amylase and lipase elevations were reported in 24% and 29% respectively. Clinical manifestation of pancreatitis was reported in < 1% of subjects across all pazopanib monotherapy studies (N=977).

1.2.1.2 Subjects with soft tissue sarcoma (STS)

1.2.1.2.1 Concluded Study VEG20002: Phase II Study of GW786034 in Patients with Relapsed or Refractory Soft Tissue Sarcoma (European Organization for Research and Treatment of Cancer [EORTC] Study)

As of 09 September 2008, enrollment was completed with 142 adult subjects enrolled. Safety and efficacy analyses were completed by the European Organization for Research and Treatment of Cancer (EORTC) and described in a synoptic clinical pharmacology study report, with effective date of 24 September 2008, and published by Sleijfer et al [19].

1.2.1.2.2 Adverse events
All 142 subjects received pazopanib 800 mg once daily. AE data were available for all 142 subjects. The most frequent clinical adverse events (AEs) (≥ 30%), regardless of causality, were fatigue (70%), nausea (46%), diarrhea (46%), hypertension (45%), decreased appetite (39%), skin hypopigmentation (37%), vomiting (36%), weight decreased (31%), dyspnea (31%), cough (30%), and constipation (30%).

1.2.1.2.3 Subjects withdrawn due to adverse events
There were 9 subjects (6.3%) who had the IP withdrawn due to an AE. Four of the 9 subjects had IP withdrawn for elevation in transaminase. Elevation in transaminase was the single most common cause of IP discontinuation. Other events that lead to discontinuation of IP were disseminated intravascular coagulation (DIC), pulmonary embolism, hypertension, hemoptysis and severe back pain, and bowel perforation with peritonitis.

1.2.2 Pazopanib Efficacy in Sarcoma

Final efficacy data for the phase II study (VEG20002) of GW786034 in patients with relapsed or refractory soft tissue sarcoma study were

published in 2009 [19]. Treatment response data are available for 138 subjects who received pazopanib 800 mg once daily. Ninety-nine percent of subjects had received prior chemotherapy: 35 subjects (25%) had received therapy in a (neo)-adjuvant setting, 83 (59%) had received therapy in an advanced setting, and 22 (16%) had received both.

The primary endpoint was the progression-free rate, using Response Evaluation Criteria in Solid Tumors (RECIST) at 12 weeks after start of treatment. Patients with leiomyosarcoma, synovial sarcoma and "the other types of sarcoma" strata receiving pazopanib in VEG20002 experienced a 12 week progression free rate of ≥ 40%, the pre-defined threshold indicating anti-tumor activity. The liposarcoma stratum did not meet its prespecified endpoint at the end of stage 1 and did not progress to stage 2. Based on the results of the VEG20002, a Phase III randomized, double blind, placebo controlled study (VEG110727) of pazopanib versus placebo in subjects with soft tissue sarcoma (study excluded patients with GIST or liposarcoma) was initiated in 2008. VEG110727 has completed patient enrollment and data are expected in 2011.

1.3 Study Rationale

Pazopanib has shown encouraging activity in a previous phase II trial in certain sarcoma subtypes. In the phase II trial of pazopanib as described above, conducted by the EORTC, the progression free rate at 12 weeks exceeded 40% for patients with leiomyosarcomas, synovial cell sarcomas, and other eligible sarcomas, but not liposarcomas. In the group of other sarcomas, five were described as vascular sarcomas.

We hypothesize that pazopanib will have therapeutic activity in angiosarcoma because they are derived from endothelial cells[1], and pazopanib is an anti-angiogenic agent. In addition, agents with anti-angiogenic properties have shown single agent activity in this disease. Sorafenib has been shown to have a 14% response rate in angiosarcomas in previously treated patients in the phase II setting[12]. Bevacizumab has demonstrated a 12% response rate [13]. Given the limited data on the activity of pazopanib in angiosarcomas, we propose to evaluate its activity in patients with angiosarcoma.

1.4 Correlative Testing

Pazopanib is believed to function as an anti-angiogenic agent given its activity against the VEGFR 1-3 as well as PDGFRA and B kinases. We hypothesize that the agent will be effective in tumors that are undergoing angiogenesis. Angiosarcoma is derived from endothelial cells and its growth has been shown to be inhibited by anti-angiogenic agents, and thus the tumor itself appears to mimic angiogenesis. However, it would be clinically useful to be able to predict whether a tumor will or will not respond to angiogenic inhibitors, as well as have an early read out on efficacy of such an agent prior to evidence of response from size

based imaging techniques such as CT or MRI. Reliable means of potentially predicting this are in development, but have not been studied systematically. We therefore propose to explore the ability of PET imaging with [F-18] FDG PET/CT to assess angiosarcomas prior to and following ongoing therapy with pazopanib to determine changes in metabolic response as an early marker of response to pazopanib.

2.1 Objectives

2.2 Primary

To determine the Progression Free Survival (PFS) at 3 months and response rate defined as Complete Response (CR) and Partial Response (PR) in angiosarcoma patients treated with pazopanib.

2.3 Secondary

1) To assess overall survival of patients treated with pazopanib.
2) To gather more safety data for pazopanib in this patient population.
3) To explore the ability of [F-18] FDG PET/CT imaging to assess response

3.1 Study Plan

3.2 Description of study design, population and duration of study therapy

This is a phase II single arm study of pazopanib in patients with angiosarcoma. The dual primary endpoints are response rate and PFS at 3 months. Success of either end-point at interim analysis will allow the study to move forward. Approximately 30 patients will be enrolled in this study at about 5 institutions. Patients will continue on treatment until progression, intolerable toxicity or withdrawal of consent.

4.1 Selection of Patients

Deviations from inclusion and exclusion criteria are not allowed because deviations can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.2 Inclusion Criteria

4.2.1. Subjects must provide written informed consent and HIPAA consent prior to performance of study-specific procedures or assessments and must be willing to comply with treatment and follow-up.
Note: Informed consent must be obtained prior to start of the specified screening window.
Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study such as bone scan) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.

4.2.2. Age ≥ 18 years.

4.2.3. Histologically or cytologically proven diagnosis of advanced stage angiosarcoma that is not amenable to treatment with curative intent. Specify site of origin as cutaneous vs. non-cutaneous.

4.2.4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.

4.2.5. Must have measurable disease per RECIST v.1.1 or cutaneous disease amenable to serial measurements. A measurable lesion is defined as a lesion that can be accurately measured in at least one dimension with the longest diameter ≥ 10 mm with CT scan. Lesions that have been treated with therapeutic intent will be considered measurable if they have increased in size by more than 20%.

4.2.6. Adequate organ system function as defined in Table 4.1 below.

Table 4.1 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 10^9/L
International normalized ratio (INR)[b]	≤1.2 X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Hepatic	
Total bilirubin[c]	≤1.5 X ULN (May not have abnormalities in both bilirubin and transaminases)
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[c]	≤2.5 X ULN May not have abnormalities in both bilirubin and transaminases)
Renal	
Serum creatinine	≤1.5 mg/dL (133 µmol/L)
Or, if serum creatinine >1.5 mg/dL: Calculated creatinine clearance (Cl_{CR}) **(Appendix B)**	≥50 mL/min
Urine Protein to Creatinine Ratio (UPC; **Appendix C**)[d]	<1

a. Subjects may not have had a transfusion within 7 days of screening assessment.
b Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
c Concomitant elevations in bilirubin and AST/ALT above ULN (upper limit of normal) are not permitted.
d If UPC ≥ 1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible.

4.1.7 Able to swallow pills whole and retain oral medication

4.1.8 A female is eligible to enter and participate in this study if the following apply:

Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had:

- A hysterectomy
- A bilateral oophorectomy (ovariectomy)
- A bilateral tubal ligation
- Is post-menopausal

Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value > 40 mIU/mL and an estradiol value < 40pg/mL (< 140 pmol/L).

Subjects using HRT must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT

Childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment and for 3 months after the completion of treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product
- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of levonorgestrel.
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the **female subject's entry** into the study, and this male is the sole partner for that subject.
- Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository)

Female subjects who are lactating must discontinue nursing prior to the first dose of study drug and refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug

4.1.10 A male is eligible to enter and participate in this study if he and his female sexual partner in the reproductive age group agree to use effective methods of contraception.

4.2 Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

4.2.1. Prior malignancy:

Subjects with a history of a prior malignancy other than angiosarcoma who have been disease-free for at least 2 years prior to the first dose of study drug and/or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.

4.2.2. History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medications for 3 months prior to first dose of study drug. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases.

4.2.3. Clinically significant gastrointestinal (GI) abnormalities that may increase the risk for GI bleeding including, but not limited to:

- Active peptic ulcer disease
- Known intraluminal metastatic lesion/s with risk of bleeding
- Inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), or other GI conditions with increased risk of perforation
- History of abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.
- Clinically significant (≥ ½ teaspoon) hemoptysis or gastrointestinal hemorrhage in the past 6 months

4.2.4 Evidence of active bleeding or bleeding diathesis. Recent hemoptysis (≥½ teaspoon of red blood within 8 weeks before first dose of study drug).

4.2.5 Clinically significant GI abnormalities that may affect absorption of investigational product including, but not limited to:

- Malabsorption syndrome
- Major resection of the stomach or small bowel

4.2.6 Corrected QT interval (QTc) > 480 msecs using Bazett's formula (Appendix E)

4.2.7 LVEF < 50%

4.2.8 History of any one or more of the following cardiovascular conditions within the past 6 months:

- Cardiac angioplasty or stenting
- Myocardial infarction
- Unstable angina
- Coronary artery bypass graft surgery
- Symptomatic peripheral vascular disease
- Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA; Appendix D)

4.2.9. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥ 140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg].
Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood pressure (BP) must be re-assessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between anti-hypertensive medication initiation or adjustment and BP measurement. These three values will be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean SBP / DBP ratio must be < 140/90 mmHg in order for a subject to be eligible for the study. Triplicate BP measurements must be performed at screening and on Cycle 1 Day 1 prior to starting treatment. (see Table 6.1 for details on BP control and re-assessment).

4.2.10. Cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or **untreated** deep venous thrombosis (DVT) within the past 6 months.
Note: Subjects with recent DVT who have been therapeutically coagulated for at least 6 weeks are eligible.

4.2.11. Major surgery or trauma within 28 days prior to first dose of investigational product and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major surgery).

4.2.12. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels (Note: tumor abutting the vessel is acceptable, but contiguous tumor and vessel is not; CT with contrast is strongly recommended to evaluate such lesions).

4.2.13 Abnormal serum calcium, magnesium, or potassium levels .

4.2.14. Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures.

4.2.15. Use of any prohibited medication within the timeframes as listed in Section 5.3.3.

4.2.16. Treatment with any of the following therapies:

- Radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of pazopanib OR

- Chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib

- Patients who require chronic use of strong CYP3A4 inhibitors or inducers including but not limited to grapefruit juice. Please see section 5.3 for additional detail.

4.2.17. Any ongoing toxicity from prior anti-cancer therapy that is > Grade 1 (except hemoglobin value; see Table 4.1) and/or that is progressing in severity, except alopecia.

4.2.18. Previous exposure to pazopanib or a VEGFR targeted kinase therapy, except for bevacizumab or VEGFR-Trap (Aflibercept).

4.2.19. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib.

4.3 Inclusion of Women and Minorities

Both men and women and members of all races, sexual orientation and ethnic groups are eligible for this study.

4.4 Patient Registration

Eligible patients will be entered on study centrally by the Fox Chase Cancer Center Office Quality Assurance (QA) Coordinator or their designee. Following registration, patients will begin protocol treatment within 7 days of registration. Issues that would cause treatment delays must be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study will be cancelled and the subject will be replaced. The QA Coordinator will be notified of cancellations as soon as possible.

Subjects may be registered from 9:00 am to 5:00 pm by calling the QA Coordinator at 215-728-4770. The investigator or designee will then fax the completed registration form, informed consent and HIPAA signature pages, and eligibility checklist to 215-214-1511. The QA Coordinator will notify the site by phone and fax when registration is confirmed and the sequence number has been assigned. Subjects must be registered and have received a sequence number assigned by the QA Coordinator prior to the initiation of treatment. The following forms must be completed at the time of registration:

- Signed and dated informed consent form
- Signed and dated HIPAA consent form
- Registration form
- Signed eligibility checklist

Exceptions to the current registration policies will not be permitted as well as:

- Late registrations (after initiation of treatment)

- Exceptions to eligibility requirements
- Participation by an institution/member not identified as eligible
- Non-Compliance with regulatory paperwork

5.1 Treatment Plan

Treatment will be administered on an out-patient basis. Treatment will be administered as described below. Dose delays and modifications will only be done following protocol guidelines described in section 6.0. If treatment delays are > 28 days study therapy will be discontinued. Each treatment cycle after cycle 1 is 21 days +/- 5 calendar days for holidays, inclement weather and/or other scheduling conflict. Treatment should continue during the 5 day window for cycle evaluation should a particular cycle need to be extended due to a scheduling conflict.

5.2 Treatment Administration

Table 5.1

Agent	Precautions	Dose	Route	Schedule	Cycle Length
Pazopanib	Orally without food at least one hour before or two hours after a meal.	200 mg x 4 (or 400 mg x 2) total dose 800 mg	PO (time of day the tablets are taken should be relatively constant)	Daily	21 days (3 weeks) +/- 5 Calendar Days

Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in area under the plasma drug concentration curve (AUC) and maximum observed plasma drug concentration (C_{max}).
Pazopanib should be taken orally without food at least one hour before or two hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant.

If a subject misses a dose, the subject should take the dose as soon as possible, but not less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled.

If a subject vomits after taking pazopanib, the subject will be instructed not to take another dose that day. The subject will resume taking pazopanib at the next scheduled dose. If vomiting persists, the subject will be instructed to notify the investigator.

5.3 Dosing Rationale

Pazopanib 800 mg once daily is the recommended monotherapy dose based on clinical and preclinical results. Once daily doses of 50 mg to 2000 mg pazopanib were investigated in the "First Time in Human", Phase I Study VEG10003.(IB RR2002/00017/10) Increases in the pazopanib dose above 800 mg once daily when administered in the fasted state did not result in a consistent increase in systemic exposure at steady-state. Therefore, no further benefit is expected at pazopanib doses above 800 mg once daily.

Pharmacodynamic data indicate that pazopanib, at a monotherapy dose of 800 mg once daily, results in effects consistent with inhibition of the VEGF receptors it was designed to target. Concentration-effect relationships were observed between trough plasma pazopanib concentrations and the development of hypertension in Study VEG10003 and the percent change from baseline in sVEGFR2 nadir in Study VEG102616. The trough plasma pazopanib concentrations associated with one-half the maximal effect (EC_{50}) in both concentration-effect relationships were similar (21.3 µg/mL and 15.3 µg/mL) and demonstrate that there is a consistent inhibition of VEGF receptor(s) in subjects with cancer when plasma pazopanib concentrations are maintained above 15 µg/mL. The plasma pazopanib EC_{50} values for biologic effects observed in the clinical studies are similar to the plasma concentration of 40 µM (17.5 µg/mL) required for optimal inhibition of VEGFR-2 phosphorylation in mice [GSK Report RH2003/00005/00].

Progression Free Survival (PFS) in subjects with renal cell cancer in Study VEG102616 was compared between subjects whose trough plasma pazopanib concentrations (C_{min}) at Week 4 were above or below selected threshold values. The deciles of the observed C_{min} values were selected as threshold values so that approximately equal numbers of subjects were included in each C_{min} interval. Subjects with a C_{min} at Week 4 above the threshold values had significantly better PFS, compared to the remaining subjects, when the threshold concentrations were 12.6 µg/mL, 17.4 µg/mL, and 20.6 µg/mL. Use of thresholds higher than 21 µg/mL did not result in a significant improvement in PFS between patients with C_{min} values above and below the threshold. Patients with C_{min} concentrations above 20.6 µg/mL also had a significantly better response rate and tumor shrinkage than the remaining patients.

Pazopanib C24 at steady-state was greater than 15 µg/mL in 93% of subjects who received 800 mg once daily in Study VEG10003. Individual subjects receiving pazopanib doses below 800 mg once daily can achieve plasma concentrations over 15 µg/mL, albeit at a lower frequency compared with what is observed at 800 mg once daily. Therefore, the pharmacokinetic and pharmacodynamic results across clinical studies demonstrate that pazopanib 800 mg once daily results in plasma concentrations that provide optimal biologic effects associated with VEGFR inhibition in the greatest proportion of subjects.

5.3 Concomitant Medications, supportive care and excluded therapies and restrictions

5.3.1 Permitted Medications

All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the 2 weeks prior to Screening. The investigator must be informed as soon as possible about any new medication(s) taken from the time of Screening until the completion of the post-treatment follow-up visit.

All concomitant medications taken during the study will be recorded in the case report form (CRF) with indication, dose information, and dates of administration.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, analgesics, erythropoietin (per ASCO guidelines), or bisphosphonates, when appropriate.

Antiemetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) may be administered prophylactically in the event of nausea. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea. (See Appendix F for Supportive care guidelines for nausea/vomiting and diarrhea) Although acetaminophen at doses of ≤ 2 g/day is permitted, it should be used with caution in subjects with impaired liver function. Glucocorticosteroids may be used as antiemetics and megestrol acetate may be used for appetite.

5.3.2 Permitted Medications – Use with Caution

Specific recommendations regarding anticoagulants:

Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib has no effect on the metabolism of S-warfarin. Hemorrhagic events, however, have been reported in clinical studies with pazopanib; therefore, pazopanib should be used with caution in subjects with increased risk of severe bleeding or who are receiving concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin). Subjects taking concomitant anticoagulant therapy should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes.

Specific recommendations regarding hypoglycemic therapy including insulin:

Results from drug-drug interaction studies conducted in subjects with cancer suggest that there will be no clinically relevant pharmacokinetic interaction between pazopanib and hypoglycemic agents. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in subjects treated with another small molecule tyrosine kinase inhibitor, sunitinib [20]. Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects will be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose will be tested during treatment with pazopanib as outlined in section 9.2 study calendar and as clinically indicated.

5.3.2.1 The Effects of Pazopanib on Other Drugs

In vitro data indicate that pazopanib is a potential inhibitor for CYP3A4, CYP2C8, CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2A6, CYP2B6, and CYP2E1. Pregnane X receptor transient transfection assay suggested some potential for human CYP3A4 induction at high concentrations. Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 *in vivo*, but had no clinically relevant effect on CYP1A2, CYP2C9 or CYP2C19 metabolism. Therefore, concomitant use of pazopanib with certain medications (substrates of CYP3A4, CYP2C8, and CYP2D6) with a narrow therapeutic window will be undertaken with **CAUTION** due to the potential for alterations in the pharmacologic effects of these medications or an increased risk for serious or life threatening adverse events associated with such medications (see below) secondary to the inhibition of specific CYP enzymes by pazopanib. In addition, the potential for drug interaction with such medications, although diminished, may persist after the last dose of pazopanib due to its long half-life (i.e., mean 30.9 hours); therefore, continue to exercise **CAUTION** for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications. These medications include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)

- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsades de Pointes)
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

5.3.2.2 The Effects of Other Food and Drugs on Pazopanib

Results from *in vitro* studies suggest that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Furthermore, *in vitro* data suggest that pazopanib is a substrate for p-glycoprotein. Substances that induce or inhibit CYP3A4 may alter the pharmacologic effects of pazopanib and will be used with **CAUTION**.

Foods and medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. **Co-administration of strong CYP3A4 inhibitors is prohibited** (see Section on Prohibited Medications); therefore selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

CYP3A4 inducers may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Drugs that induce CYP3A4 and may decrease pazopanib plasma concentrations include (but are not limited to):

- Glucocorticoids: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)
- Anticonvulsants: phenytoin, carbamazepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentine
- Miscellaneous: St. John's Wort, modafinil, pioglitazone

5.3.3 Prohibited Foods and Medications

Subjects must not receive other anti-cancer therapy [cytotoxic, biologic, radiation, or hormonal (other than leuprolide or other GnRH agonists)] while on treatment in this study.

Foods and medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is **PROHIBITED** beginning **14** days prior to the first dose of study drug until discontinuation from the drug. **Strong CYP3A4 inhibitors include (but are not limited to)**:

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, lopinavir)
- Antifungals: itraconazole, ketoconazole, voriconazole
- Antidepressants: nefazodone
- Grapefruits and grapefruit juice

Foods and medications that induce CYP3A4 are **PROHIBITED** beginning **14** days prior to the first dose of study drug until discontinuation from the drug.

Subjects must not receive any other investigational drug within 15 days of the last dose of pazopanib.

5.4 Duration of Therapy

Subjects will receive study treatment until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events (including meeting stopping criteria for liver chemistry or for hematologic and other non-hematologic toxicity defined in Section 6.0)
- Treatment held > 28 days
- Patient required > 2 dose modifications
- Patient becomes pregnant
- Patient decides to withdraw from the study
- Study is closed or terminated

- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Duration of Follow up

After discontinuation of the study treatment, subjects will remain on the study for follow-up assessments of disease status and updates on anti-cancer treatments until death or for a maximum of two years from the date of the last subject enrolled. Patients removed from study for unacceptable study related adverse events requiring discontinuation of the study treatment will be followed until resolution or stabilization of the adverse event.

5.6 Criteria for discontinuation

Patients will be removed from study when any of the criteria listed in Section 5.4 applies or if they are lost to follow-up. In addition deviation(s) from the protocol may be a cause for discontinuation. The primary reason for study removal and the date the patient was removed must be documented in the medical record and case report form. If treatment is discontinued for a scheduled surgery, pazopanib must be held at least 7 days prior to the scheduled surgery.

6.1 Dose modifications

6.2 General principles

At each visit during the Treatment Period, subjects will first be evaluated for the occurrence of AEs and laboratory abnormalities. The potential causes of the AEs will be thoroughly investigated and confounding factors identified and eliminated whenever possible. Some AEs, although rare, can result in significant clinical consequence such as arterial/venal thrombosis, severe hemorrhage, bowel perforation and severe fatigue/asthenia, therefore will be promptly identified and managed.

Should a patient require scheduled surgery while on study, pazopanib must be discontinued for at least 7 days prior to surgery. Following the surgery, adequate would healing must be determined by the treating physician, in order for the patient to resume pazopanib treatment in this trial.

The National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE, v.4) must be used to Grade the severity of AEs except for hypertension and palmar-plantar Erythrodysesthesia Syndrome: grading for these events is described in the table below. Specific recommendations for management of these possible AEs along with guidelines for dose interruption, modification, or discontinuation are provided in Table 6.1 for pazopanib. In the event of treatment emergent hepatotoxicity, the guidelines for management of

hepatotoxicity provided in Table 6.2 will be followed. Dose reductions are permanent; there are no dose re-escalations. Patients requiring > 2 dose reductions must discontinue protocol treatment. Patients requiring treatment to be held > 28 days must discontinue protocol treatment. Treatment will be held for ≥ grade 3 toxicity except alopecia. Hold until ≤ grade 1 then dose reduce 1 level.

6.3 Dose Interruptions/Modifications for Specific, Non-liver Related, Toxicities

If dose reduction is necessary, two dose reductions will be permitted (unless otherwise noted in Tables 6.1 and 6.2) in a stepwise fashion (initially to 600 mg po daily and subsequently to 400 mg po daily if necessary; 400 mg po daily will be the minimum dose level) according to **Table 6.1**.

Table 6.1 Dose Modification Algorithms for Potential Treatment-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(A). Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg). (Grade 2)	(1) Continue pazopanib at the current dose. (2) Adjust current or initiate new antihypertensive medication(s). (3) Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Well-controlled BP defined as SBP <140 mmHg and mean DBP <90 mmHg. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(B). Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A). (Grade 3)	(1) Consider reducing or interrupting pazopanib as clinically indicated. (2) Adjust current or initiate new antihypertensive medication(s). (3) Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. (4) Once BP is well-controlled (≤ 140/90), restart pazopanib dose-reduced by 200 mg if pazopanib was interrupted.
(C). Symptomatic hypertension or recurring SBP ≥160 mmHg, or DBP ≥100 mmHg, despite modification of antihypertensive medication(s) (Grade 3)	(1) nterrupt pazopanib. (2) Adjust current or initiate new antihypertensive medication(s). (3) Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. (4) Once BP is well-controlled, restart pazopanib dose-reduced by 200 mg.
(D). Refractory hypertension unresponsive to above interventions	Discontinue pazopanib and continue follow-up per protocol.
Prolongation of QTc Interval:	
QTc ≥ 480 < 500 msec	Continue pazopanib at the current dose; monitor as clinically indicated.
QTc ≥ 500 msec	Discontinue pazopanib and continue follow-up per protocol.
Proteinuria	
UPC < 3	Continue pazopanib at the current dose; monitor as clinically indicated
UPC ≥ 3 or 24-h urine protein ≥ 3g	(1) nterrupt pazopanib. (2) Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is < 3 grams. Then restart pazopanib dose-reduced

AE Terms & Descriptions	Dose Modification Algorithms
	by 200 mg. (3) f UPC > 3 or 24-h urine protein ≥ 3g recurs, repeat steps 1 and 2 (4) f UPC ≥ 3 or 24-hr urine protein ≥ 3g recurs and the pazopanib dose can no longer be reduced, discontinue pazopanib and continue follow-up per protocol.
Hemorrhage /Bleeding: Investigate and document underlying etiology of the bleeding	
Grade 1	For hemoptysis, interrupt pazopanib and contact the Principal Investigator to discuss whether further treatment with pazopanib is appropriate. For other Grade I hemorrhage/bleeding events, continue pazopanib at the current dose; monitor as clinically indicated.
Grade 2	(1) f pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol. Otherwise, interrupt pazopanib until the AE resolves to ≤ Grade 1. (2) Restart pazopanib; consider reducing dose and monitor as indicated.
Grade 3 or 4, or recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue pazopanib and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue pazopanib at the current dose; monitor as clinically indicated
Grade 3	(1) nterrupt pazopanib treatment. (2) nitiate and monitor anticoagulation as clinically indicated. (3) Resume pazopanib treatment at the same dose only if all of the following criteria are met: - The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week. - No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Subject will be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, INR will be monitored within three to five days after any change in pazopanib dosing (e.g., re-initiating, escalating/de-escalating, or discontinuing pazopanib), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation.
Grade 4 and/or PE	Discontinue pazopanib and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue pazopanib and continue follow-up per protocol.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1 or 2	Continue pazopanib with current dose; monitor as clinically indicated.
Grade 3 or 4	(1) nterrupt pazopanib until toxicity resolves to ≤ Grade 2. (2) estart pazopanib dose-reduced by 200 mg and monitor as clinically indicated. If recurrent, further dose reduce to 400 mg po daily. If no recovery to ≤ Grade 2 or in the event of recurrent Grade 3 or 4 thrombocytopenia, discontinue pazopanib and follow-up per protocol.

AE Terms & Descriptions	Dose Modification Algorithms
Anemia:	
No specific dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above.	
Palmar-plantar Erythrodysesthesia Syndrome	
Grade 1 Minimal skin changes or dermatitis without pain (erythema, edema, hyperkeratosis)	(1) Continue pazopanib at present dose (2) nitiate supportive care with emollient lotions
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, edema, bleed, hyperkeratosis)	(1) Hold pazopanib (2) Treat as clinically appropriate: emollient lotions, limiting tight shoes and heels (3) Upon resolution to Grade 1 or better, restart pazopanib with a dose reduction to 600 mg (4) f recurrent consider a further dose reduction to 400mg or discontinuation
Grade 3 Severe skin changes with pain and limiting self care ADLs	(1) Discontinue pazopanib
Other Clinically Significant Adverse Events	
Grade 1	Continue pazopanib; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	(1) nterrupt pazopanib until toxicity resolves to ≤ Grade 1. (2) Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated. If recurrent, further dose reduce to 400 mg po daily.
Grade 4	Discontinue pazopanib and continue follow-up per protocol.

6.4 Dose Interruptions/Modifications for Hepatotoxicity

Recommendations for pazopanib dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided in Table 6.2. As a general rule, since many subjects are taking multiple concurrent medications, it is critical to (a) do a thorough evaluation of the subject's concurrent medications (ensuring all are recorded in the CRF), and (b) identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary. Record alcohol use is recorded on the history and physical form in the CRF binder. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions. Imaging studies must be obtained to document potential progression of malignancy.

Table 6.2 Guidelines for Management of Treatment Emergent Hepatotoxicity

Event	Dose Modification Algorithms
(A). Grade 1: ALT/AST > ULN - 3.0 x ULN	Continue pazopanib at current dose with full panel liver function tests (LFTs)[a] monitored as per protocol. Study calendar (section 9.2)
(B). Grade 2: asymptomatic with ALT/AST > 3.0 – 5.0 x ULN; symptomatic > 3.0 without bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤ 35%) and without hypersensitivity symptoms (e.g., fever, rash)	Liver Event Monitoring Criteria: (1) Continue pazopanib at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to ≤ 3.0 x ULN.
C). Grade 3: ALT/AST > 5.0 – 20.0 x ULN; > 5.0 x ULN for > 2 weeks without bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤ 35%) and without hypersensitivity symptoms (e.g., fever, rash)	1st occurrence – Liver Event Interruption Criteria[c]: (1) Interrupt pazopanib until toxicity resolves to ≤ ULN - 3.0 x ULN or baseline. Report the event to the QA Specialist/ Study Monitor and Novartis as an SAE within 24 hours of learning of its occurrence and complete the CRF and SAE report. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and LFTs. (2) Liver imaging and other laboratory investigations will be considered as clinically appropriate. (3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to ≤ 3.0 x ULN. (4) If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose and measure serum liver tests weekly for 8 weeks.* Re-challenge may be considered if ALL following criteria are met: - ALT/AST reduced to ≤ 3.0 x ULN - Total bilirubin <1.5 x ULN or direct bilirubin ≤ 35% - No hypersensitivity signs or symptoms - Subject is benefiting from therapy. Recurrence – Liver Event Stopping Criteria[c]: Discontinue pazopanib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to ≤ 3.0 x ULN.
(D). ALT/AST > ULN - 3.0 x ULN **with** concomitant elevation in bilirubin[b] (defined as total bilirubin ≥1.5 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	Liver Event Stopping Criteria[c]: (1) Discontinue pazopanib immediately, report the event to the QA Specialist/ Study Monitor and Novartis as an SAE **within 24 hours** of learning of its occurrence (section 10.3). Make every reasonable attempt to have subjects return to the clinic for repeat liver chemistries and repeat LFTs (2) Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs[a] weekly or more frequently if clinically indicated until LFTs are reduced to ALT/AST ≤ 3.0 x ULN and Bilirubin < 1.5 x ULN.

Event	Dose Modification Algorithms
(E). For isolated total bilirubin[b] elevation without concurrent ALT/AST increases.	(1) Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT/AST or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury.. (2) If bilirubin is ≥1.5 x ULN in the absence of ALT/AST elevation, fractionation of bilirubin elevation will be performed. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis will be performed. (3) If bilirubin elevation concurrent with ALT/AST increases following treatment guidelines above based on ALT/AST value.

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, GGT, and total bilirubin. Coagulation tests will be performed as clinically indicated.
b. Serum bilirubin fractionation will be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >1.5 x ULN, then the event will be promptly reported as an SAE.
c. When a liver chemistry event meets the Liver Event Interruption Criteria, or Liver Event Stopping Criteria, blood samples will be obtained for clinical laboratory testing

ULN = upper limit of normal

7.1 Study Agent Information

7.2 Pazopanib Formulation, product identification, package and labeling

7.2.1 Product description

Pazopanib monohydrochloride salt is supplied as aqueous film-coated tablets containing either 200 mg or 400 mg of the free base. Both the 200-mg and the 400-mg tablets are oval-shaped and white in color. Refer to the pazopanib IB for information regarding the physical and chemical properties of pazopanib and a list of excipients.

7.2.2 Route of administration

Pazopanib will be taken orally without food at least one hour before or two hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant.

7.2.3 Availability

Pazopanib will be provided to the sites by Novartis. The 200-mg pazopanib tablets are packaged 34 to a bottle. The 400-mg tablets are packaged 68 to a bottle. All bottles are made of high-density polyethylene and have a child-resistant closure. Each bottle will be labeled with the protocol number, dosing and storage instructions, sponsor name and address, and the expiration date, when required. The contents of the label will be in accordance with all applicable regulatory requirements.

Pazopanib will be dispatched to the site only after receipt of required documents in accordance with applicable regulatory requirements and Novartis' procedures.

7.2.4 Storage requirements

Pazopanib must be stored in a secure, limited-access area at the study site, under the appropriate physical conditions for the product. The recommended storage conditions, and expiration date where required, are stated on the product label.

Under normal conditions of handling and administration, pazopanib is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis upon request.

7.3 Destruction of drug

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs unless otherwise specified.

7.4 Records to be kept at site, dispensing and accountability

Pazopanib must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive pazopanib, in accordance with all applicable regulatory requirements. Only the site pharmacist, Investigator, or other authorized site personnel may have access to and supply or administer pazopanib. Pazopanib will be dispensed to the subject after it has been confirmed that the subject meets all eligibility criteria and all screening assessments have been completed and the results reviewed. Subjects are to return to the site approximately every 3 weeks for re-supply of pazopanib, according to the study visit schedule (section 9.2).

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and will include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each patient, including unique patient identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).

It is recommended that the NCI Drug Accountability Record Form be utilized for drug tracking.

7.5 Treatment of Investigational Product Overdose

No maximum tolerated dose (MTD) was reached in the dose escalation study of pazopanib administered as a single agent at repeated doses of up to 2000mg/day (Study VEG10003). Systemic exposure to pazopanib at steady-state appeared to plateau at doses greater than 800 mg once daily. Increases in the daily pazopanib dose above 800 mg in the fasted state resulted in a small or no increase in mean systemic exposure to pazopanib.

In the event of pazopanib overdose (defined as administration of more than the protocol-specified dose), the investigator will contact the Principal Investigator. Decisions regarding pazopanib dose modifications or interruptions will be made by the investigator in consultation with the Principal Investigator based on the clinical evaluation of the subject.

Following an overdose, additional monitoring of the subject for AEs/SAEs and laboratory abnormalities will be considered. A plasma sample for pharmacokinetic analysis for pazopanib may be requested by the Principal Investigator on a case-by-case basis. This plasma sample will be collected as soon as possible, but within 7 days from the date of the last dose of study drug. Information regarding the quantity of the excess dose, as well as the duration of overdosing, will be documented in the CRF.

8.0 Correlative /Special Studies

8.1. Hypothesis

Pazopanib is believed to function as an anti-angiogenic agent given its activity against the VEGFR 1-3 as well as PDGFRA and B kinases. We hypothesize that the agent will be effective in tumors that are undergoing angiogenesis. Angiosarcoma is derived from endothelial cells and its growth has been shown to be inhibited by anti-angiogenic agents, and thus the tumor itself appears to mimic angiogenesis. However, it would be clinically useful to be able to predict whether a tumor will or will not respond to angiogenic inhibitors, as well as have an early read out on efficacy of such an agent prior to evidence of response from size based imaging techniques such as CT or MRI. Reliable means of potentially predicting this are in development, but have not been studied systematically. We therefore propose to explore the ability of PET imaging with [F-18]RDG-K5 to assess angiosarcomas prior to and following ongoing therapy with pazopanib to determine changes in angiogenesis as an early marker of response to pazopanib as compared with [F-18] FDG PET/CT and CT imaging.

8.2. Preliminary Data

[F-18]RDG-K5 is a promising radiolabeled diagnostic agent for imaging of alpha v Beta 3 integrin expression, a family of integrin glycoproteins, found on newly formed blood vessels in tumors. The agent was studied in 21 normal and cancer subjects and found to have no safety concerns; Dr. Yu at Fox Chase was one of the Principal Investigators for that study. In addition, studies in patients with breast, lung, sarcoma and melanoma found good signal/background ratios. In addition, in two patients biopsies were performed from tumor samples demonstrating the presence of alpha v Beta 3 integrin expression by immune histochemistry. The agent is being studied at Fox Chase in patients treated with Bevacizumab; three patients have been accrued and are undergoing initial baseline studies.

8.3. Correlative Study Design

All patients at treated at Fox Chase Cancer Center will participate in these correlative studies. Patients will have [F-18] FDG PET/ CT imaging acquired at baseline and then following therapy with pazopanib for approximately 3 weeks. Imaging will be compared to baseline imaging with CT/MRI or physical exam measurements determined at baseline and at 12 weeks.

8.3.1. Study Population

All patients treated at Fox Chase Cancer Center on the phase II trial of Pazopanib

8.3.2 Methodology

[F-18] Fluorodeoxyglucose injection is a radiopharmaceutical containing no-carrier added radioactive 2-deoxy-2-[F-18]fluoro-D-g1ucose, which is used for diagnostic purposes in conjunction with PET imaging. It is administered by intravenous injection. Currently, it is the radiopharmaceutical used the majority of the time with PET imaging. It has an uptake phase of approximately 60 to 90 minutes.
Information from the baseline and 3 weeks of treatment of [F-18] Fluorodeoxyglucose PET/CT scans will be reviewed, evaluated and recorded for:

- location of the lesion(s), specific diagnosis, and confidence in diagnosis
- tumor uptake or non-tumor uptake
- standard uptake values (SUV)
- tumor to background ratio

Tumor size from baseline and at 12 weeks diagnostic CT will be recorded and change in tumor response determined by routine computer processing techniques. If a contrast agent was used during the diagnostic CT, the Hounsfield units will be recorded and evaluated for change in tumor density. Documentation and follow up of cutaneous lesion(s) response(s)

will be evaluated by the medical oncologist at baseline and at 12 weeks of treatment.

8.3.3 Analytic plan

The objective of the study is to examine how [F-18] FDG PET/CT as an imaging agent may be able to predict efficacy or early response as compared with CT imaging. Analyses will be made by Dr. Yu at Fox Chase Cancer Center utilizing individual lesions with a minimum of one lesion per patient up to a maximum of five lesions per patient. Given the patient population with metastatic disease, it is anticipated we will be analyzing up to 50 lesions. PET images will be scored using the following criteria:
Score = 0 Disease progression (< - 20%); Defined as the percentage change in SUV values in each paired image assessment to be less than a negative 20%, when baseline images are compared to week 4 images
Score = 1 No response (20% to > - 20%); Defined as the percentage change in SUV values in each paired image assessment to be less than 20% up to greater than or equal to a negative 20%, when baseline images are compared to week 4 images
Score = 2 Partial response (≥ 20% to < 50%); Defined as the percentage change in SUV values in each paired image assessment to be between > 20% and < 50%, when baseline images are compared to week 4 images
Score = 3 Successful response (≥ 50% to <90%); Defined as the percentage change in SUV values in each paired image assessment to be between > 50% and < 90%, when baseline images are compared to week 4 images
Score = 4 Complete response (≥ 90%); Defined as the percentage change in SUV values in each paired image assessment to be >90%, when baseline images are compared to week 4 images CT imaging will utilize RESIST criteria and will also document changes in Hounsfield units utilizing the baseline and the week 12 studies; if a patient progresses at the week 6 imaging time point, the week six study will be used.

If a lesion is not detected on the pre treatment [F-18] FDG PET image /CT or diagnostic CT image), the score for the paired image sets will be defined as not interpretable.

The descriptive statistics will include mean, SD, median, minimum, and maximum for continuous variables and the numbers and percentages for categorical variables. The statistical test will be two sided at the 0.05 level of significance with 95% confidence limit. The score of each variable will be calculated as an average of the lesion level score for each patient. Imaging data for SUVs, tumor to background ratios, lesion size, score will be analyzed and presented individually.

Summary statistics for changes in SUVs, tumor to background ratios,

lesion size, and comparison scores will be analyzed and presented. A paired t-test will be used to evaluate the mean changes among pre-treatment, the subsequent imaging test, and 95% confidence internal for the changes in primary endpoints will be presented.

The change in images (i.e., [[F-18]FDG PET SUV or Diagnostic CT tumor size changes) will be computed as the baseline value (pre-treatment) minus the appropriate post baseline (after mid-treatment) value. Changes from pre-treatment values in SUVs and target-to-background ratios, and qualitative scores for change in lesion uptake at each of the time-points will be explored for their ability to predict patient response to therapy.

The change in images (i.e., [F-18]FDG PET SUV or Diagnostic CT tumor size changes) will be computed as the baseline value (pre-treatment) minus the on treatment value. Changes from pre-treatment values in SUVs and target-to-background ratios, and qualitative scores for change in lesion uptake will be explored for their ability to predict patient response to treatment.

The statistic for determining the correlation between the [F-18] FDG PET/CT and other imaging modalities is the Pearson's correlation coefficient. If the assumption of normality does not hold, then Spearman's rank correlation coefficient will be computed. Pearson's correlation coefficients and the corresponding 2-sided 90% confidence intervals will be computed for the change in [F-18] FDG PET/CT and the change in Diagnostic CT from baseline to on treatment imaging (4 week/ 12 week for FDG PET and CT respectively). If the lower bound of the confidence interval is >0.4, then it will be concluded that the given pair of SUVs are correlated. In addition to Pearson's correlation coefficient, graphical displays of the data will be provided. All other secondary and exploratory correlations will be analyzed in the same manner as the primary correlations

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the

date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance will be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

9.1 Study Assessments and Procedures

A signed, written informed consent and HIPAA consent form must be obtained from the subject prior to any study-specific procedures or assessments. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol. The study assessments schedules and visit windows are summarized below. **Refer to Section 9.2, the Study Calendar for a complete list and schedule**.

9.2 Screening and Baseline Assessments

9.1.1 Assessments within 4 Weeks of the First Dose

- Baseline radiologic evaluation scan (CT/ MRI) for tumor assessment (Refer to Section 11.3)
- Correlative PET/CT (for Fox Chase Cancer Center patients only)
- Echo/MUGA

9.1.2 Assessments within 2 Weeks of the First Dose

- Demography: date of birth, race and gender.
- Medical history including:
    - Angiosarcoma specific history including: date of diagnosis, primary tumor type with histology/cytology determination, current stage of cancer, prior systemic treatment(s) for angiosarcoma, ongoing toxicity related to prior treatment(s); and history of other malignancies

- Prior surgery and/or radiotherapy (date, organ/anatomic region(s) of surgery and/or radiotherapy must be documented), other significant medical and surgical histories within the past 6 months.

- Physical examinations: height (only recorded at baseline), body weight and current medical conditions.
- Record all the medication(s) received within 2 weeks prior to the first dose of study medication and indicate if the medication is continuing.
- Vital signs: body temperature, respiratory rate, blood pressure and heart rate. At the baseline visit, blood pressure will be measured three times at approximately 2-minute intervals. All three blood pressure values will be recorded on the CRF. These three values will be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean diastolic and the mean systolic blood pressures are to be used to determine if the subject's blood pressure is within the well-controlled range (<140/90 mm Hg).

  If a subject presents with poorly controlled hypertension, defined as SBP ≥140 mmHg or DBP ≥90 mmHg, antihypertensive medication(s) will be initiated or adjusted with a goal to control the blood pressure to <140/90 mmHg.
- ECOG PS, height and weight
- Clinical laboratory assessments. Laboratory assessments will be performed as indicated in the Study Calendar in section 9.2. These assessments may be carried out within 3 days before the actual visit to allow flexibility in scheduling. Assessments may be performed more frequently if clinically indicated. Correction of electrolytes (most importantly, potassium, magnesium and calcium) to within normal ranges will take place prior to study entry and during study conduct as clinically indicated.
- 12-lead ECG with QTc measurement (Appendix E)
- Serum pregnancy test for women of childbearing potential. (Section 4.1.9)

9.1.3 Pre-first dose Eligibility Assessments

- Physical examination: to identify any changes in the subject's mental and medical conditions since baseline assessment that would make him/her ineligible for the study.
- Vital Signs including: Temperature, Pulse, Respirations and Blood pressure measurements: subjects must have a blood pressure reading of <140/90mmHg to be eligible. At the Day 1 visit, blood

pressure will be measured three times, with each measurement separated from the prior measurement by at least 2 minutes. All three blood pressure values will be recorded on the CRF. These three values will be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean diastolic and the mean systolic blood pressures are to be used to determine if the subject's blood pressure is within the well-controlled range.

It is particularly important to check the blood pressure of any subject for whom anti-hypertensive medication has been initiated and/or dosing has been adjusted during the Baseline Period. At least 24 hours must have elapsed between anti-hypertensive medication initiation or adjustment and BP measurement. If, after treatment with anti-hypertensive medication, a subject's mean diastolic and/or mean systolic blood pressure is not <140/90mmHg, then further modifications of these medication(s) may be made while the subject is still in the Baseline Period. After further anti-hypertensive treatment, the subject's blood pressure must then be rechecked to determine eligibility for the trial.

See Table 6.1 for instruction on blood pressure measurement and determination of mean blood pressure values.

- ECOG PS: Any changes since baseline assessment will be recorded in the CRF. Subjects having deterioration of ECOG PS to >2 will be excluded from the study.
- Weight
- Clinical Laboratory Assessments: Review results of all the other baseline assessments to re-confirm the subject's eligibility for the study. Any screening laboratory result outside the normal range will be repeated prior to the first dose. All laboratory results must remain within the values outlined in the Inclusion Criteria (Section 4.1), otherwise the subject is no longer eligible to participate in the study.

9.2 Study Calendar	Screening[b]	Prior to Every Cycle	Daily	Weeks 3,5,7 and 9	Even Numbered cycles	End of Therapy	Follow up[l]
Informed consent & HIPAA[a]	X						
Medical history	X						
Physical exam	X	X				X	X
Concurrent Meds	X	X				X	X
Vital signs (T, P, R, BP[h])	X[h]	X[h]				X	X
Height	X						
Weight	X	X				X	X
Performance status	X	X				X	X
PT/INR, APTT	X	X				X	X
CBC w/diff	X	X				X	X
GGT, Serum chemistry[c]	X	X[c]				X[c]	X[c]
GGT, LFT's[d]				X[d]			
Magnesium[C]	X						
β-HCG	X[e]						
TSH, free T4	X				X	X	
UPC ratio	X				X	X	
Echo/MUGA[f]	X						X
EKG[g]	X[g]	X[g]				X[g]	X[g]
Adverse Events	X	X	X[b]		X	X	
Radiologic Evaluation: CT or MRI[i, j]	X				X	X[k]	
Tumor Measurements[ij,k]	X				X	X[k]	
Correlative PET/CT	X[m]	X[m]					
Pazopanib[n]			X		X		

a: Informed consent must be signed within 30 days of registration. If signature is outside that window the patient must initial and date their original consent or sign a new consent.

b: Pre-study H&P and all labs must be ≤ 2 weeks before registration. Tumor measurements and radiologic evaluations must be < 4 weeks before study drug initiation. EKG ≤ 2 weeks before study drug initiation, ECHO/MUGA < 6 weeks before study drug initiation. Pre-study assessments may be used for C1D1 assessments if completed ≤ 2 weeks before study drug initiation. AEs are to be recorded daily as they occur by the patient on their pill diary and collected after each cycle is complete. Daily AEs does not imply that the site should contact the patient daily for this assessment.

c: Albumin, alkaline phosphatase, total bilirubin, direct bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, sodium, total protein, SGOT [AST], SGPT [ALT] and GGT. All laboratory tests with values that become clinically significant while subject is participating in study or ≤ 28 days after last dose of study drug will be repeated until values return to baseline. Magnesium must be within normal limits. Please see footnote d for cycles 2 and 3.

d: during weeks 3-9 only, obtain GGT, AST, ALT, T. Bili every other week ; liver function tests do not need to be included in the serum chemistry evaluation performed prior to cycles 2 and 3; all others chemistries as still required to be performed as per footnote c..

e: Serum pregnancy test (women of childbearing potential) must be completed ≤ 2 weeks before beginning treatment.

f: Echo/MUGA will be repeated every 12 weeks in patients who received prior anthracycline.

g: A 12-lead ECG will be obtained at Screening/Baseline, every 6 weeks during the first 6 months of the study and every 12 weeks in the next 6 months. After 1 year on study, ECGs will be performed every 6 months.

h: BP assessment are to be performed in **triplicate**, 2 minutes apart at both screening and on Cycle 1 Day 1, prior to treatment. BP assessments need only be performed 1 time on Day 1 for Cycles 2 and beyond. (section 9.1.2).

i: Pre-study imaging for CNS metastases only as clinically indicated (see Section 4.2.2)

j Response to treatment will be measured using RECIST 1.1 criteria.

k: Off-therapy evaluation. If PD documented during scheduled on-study assessment, tumor measurements and radiologic staging do not need to be repeated.

l: Subjects will be followed for clinical assessments of disease status and updates on anti-cancer treatments. The first visit should be within 3 – 4 weeks then every 3 months for a maximum of two years from the date of the last subject enrolled or until death. Patients removed from study for unacceptable adverse events related to the study treatment will be followed until resolution/ stabilization of the adverse event. Any labs or scans relating to a toxicity or disease measurement will be conducted at an interval determined by the treating physician and results will be recorded on the long term follow up case report forms.

m:	PET FDG will be done only in FCCC patients at baseline ≤ 2 weeks prior to initiation of drug therapy **and** once after 3 weeks of drug therapy
n:	Pazopanib 800 mg p.o. once daily

10.1 Adverse Event

10.2 Definitions

10.2.1 Adverse Events (AE)

An Adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011)*

10.2.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE) is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/ birth defect, or results in any important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

10.2.3 Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

- Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
- Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.

- Grade 4: Life-threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE

10.2.4 Attribution/Relationship to study drug

- Definite – clearly related
- Probable – likely related
- Possible – may be related
- Unlikely – doubtfully related
- Unrelated – clearly not related

10.2.5 Expectedness

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or
2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event.
   (OHRP Guidance on reviewing unanticipated problems 2007)

10.3 Recording Responsibilities

10.3.1 Investigative site recording responsibilities:

Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.

All AEs and SAEs will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. All events will be recorded on case report forms for the duration of the study until they resolve.

All SAEs will be recorded on the FDA MedWatch form 3500a or other sponsor-designated SAE reporting form After submitting the initial report

it may be necessary to submit follow up reports to the QA Specialist/ Study Monitor should the event require further investigation.

10.4 Reporting Responsibilities

10.4.1 Investigative site reporting responsibilities:

- The investigator/ site is responsible to report all SAEs to the the QA Specialist/ Study Monitor within 24 hours of becoming aware of the event. A written report must follow within 48 hours.
- Each investigator is responsible to report all AEs/SAEs to their local IRB following guidelines set by that IRB. Fox Chase Cancer Center reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent to Extramural Research Program (ERP) Regulatory Coordinator.
- If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the ERP, draft revisions will be made in track changes and submitted to for consideration. Any consent revisions must receive ERP approval **prior** to submission to the IRB.
- Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the QA Specialist / Study Monitor who will review and verify the particular AE's reporting requirements with the Principal Investigator.
- If the results of an investigator or ERP investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.
- Copies of all related correspondence and reporting documents must be submitted to the ERP Regulatory Coordinator and will be maintained in a regulatory file.

The participating site should report events to:
Quality Assurance Specialist / Study Monitor
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia PA 19111
Phone: 215-214-3704
Fax: 215-214-1511

10.4.2 Extramural Research Program (ERP) Reporting Responsibilities:

Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.

i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
ii. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
iii. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from ERP for each site's IRB of record along with the report of the adverse event.

SAEs that related, unexpected, fatal, or life-threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions are as directed by FDA guidelines (http://www.fda.gov/medwatch/index.html). Serious, unexpected events that suggest significant clinical risk will be submitted to within 15 calendar days after initial receipt of this information.

Food and Drug Administration:
Telephone 1-800-FDA-1088
Fax 1-800-FDA-0178
http://www.fda.gov/medwatch/report.htm

Mandatory Drug Reporting:
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Office of Post-Marketing Drug Risk Assessment (HFD 730)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

(301) 827-3169 for any further questions regarding where to send drug mandatory reporting forms

Reporting to Novartis and NCCN:
Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, will be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported. Follow-up information will be forwarded to Novartis within 24 hours.

All serious adverse events will be reported by the QA Specialist / Study Monitor by facsimile within 24 hours to Novartis.
Novartis Patient Safety Fax: (877) 778-9739

And

NCCN via fax at 215-358-7699 or e-mailed to ORPReports@nccn.org

SAEs brought to the attention of the Quality Assurance Specialist / Study Monitor at any time after cessation of pazopanib and considered by the investigator to be related or possibly related to pazopanib will be reported to Novartis if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until the follow up period is ended.

In addition, the Investigator will adhere to the safety reporting requirements and timelines described in the Clinical Trial Agreement with National Comprehensive Cancer Network (NCCN).

10.5 Pregnancy

All WOCBP will be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

In the event of a confirmed pregnancy in a patient participating in the study, the Investigator must immediately notify the QA Specialist / Study Monitor who will either notify or have their designee notify Dr. von Mehren, the Principal Investigator and Novartis.

11.1 Measures of Effect

Response Evaluation Criteria in Solid Tumors (RECIST)

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria will be used for objective tumor response assessment. Assessments will be performed *after every two cycles* of treatments. Once protocol treatment has been completed subjects will be assessed every three months or sooner as indicated and judged by treating physicians.

11.2 Definitions.

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.

11.3 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 ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. 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. Sarcomas arising in a previously irradiated site will be considered measurable. Sarcoma lesions that have been treated with therapeutic intent will be considered measurable if they have increased in size by more than 20%.

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 will 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, will be identified as **target lesions** and recorded and measured at baseline. Target lesions will 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 which can be measured reproducibly will 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 will be identified as **non-target lesions** and will also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each will be noted throughout follow-up.

11.4 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will 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 will 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.

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 will be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

As with CT, if an MRI is performed, the technical specifications of the scanning sequences used will be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up will be the same as was used at baseline and the lesions will 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 will be used and the image acquisition protocol will be followed as closely as possible to prior scans. Body scans will be performed with breath-hold scanning techniques, if possible.

11.5 Response Criteria

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

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 will prevail in such circumstances, and the progression status will be confirmed at a later time by the review panel (or Principal Investigator).

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)

Table 11.1

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** 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 will 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)

Table 11.2

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.6 Duration of Response

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

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

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

11.6.1 Progression-Free Survival

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

11.6.2 Response Review

Patients that have a CR or PR by RECIST 1.1 may have the imaging studies documenting that response centrally reviewed by the department of radiology in coordination with the study PI Dr. Margaret von Mehren. If requested, baseline, the initial response image and the confirming scan must be forwarded in DICOM format to the QA Specialist / Study Monitor for review.

12.1 Statistical Considerations

12.2 Study Design/Endpoints

This study's primary objective is to estimate the chance of Progression Free Survival at 3 months and test the hypothesis that it exceeds 5% in angiosarcoma patients treated with pazopanib. The secondary objectives are to estimate the response rate (RR) defined as Complete Response (CR) and Partial Response (PR) in angiosarcoma patients treated with pazopanib, to assess overall survival of patients treated with pazopanib and to gather more safety data for pazopanib in this patient population. Additionally, Fox Chase Cancer Center, alone; will explore the ability of PET with RGD-5 and FDG imaging to assess response.

Using a Simon design with n1=15, n2=30, we will submit 15 patients initially and evaluate them for response and any time up to 3 months. If at least 1/15 patient responds, then another 15 patients will be recruited. If at least 4/30 patients respond we will reject the null of 5% response and accept the 20% alternative. Otherwise, the study will be terminated after the initial 15 patients are evaluated and the null hypothesis accepted. The study has 46% chance of early stopping under the null, 3.5% under the alternative. It has overall 86% power and 5.8% type I error.

12.3 Early stopping for excessive toxicity

We will test the hypothesis that grade 4 toxicity (despite maximum supportive care) is at most 5% versus the alternative that it is a least 25% .The design will have a 54% chance of early stopping if the true toxicity is at least 25% and 0.6% chance of early stopping in error. It will declare the treatment too toxic with 82% power if the true toxicity is at least 25%. The study will be terminated early if ever 4 of the initial 15 patients have grade 4 or higher toxicity despite maximum supportive care. Similarly, if at any point 6 patients have grade 4 or higher toxicity the study will also be terminated and declared too toxic. Properties of the stopping rule and final decision rule are tabulated below.

	Table entries as percents						
True toxicity	10	15	20	25	30	35	40
p(early stop)	6	18	35	54	70	82	91
p(decision)	10	33	61	82	93	98	99

p(early stop): chance that trial is terminated for excess toxicity at or before 15 patients are evaluated.

p(decision): chance that treatment is declared too toxic either early or at the latest after patient 30 has been evaluated.

12.2.1 Methods of data analysis

At completion PFS and OS will be estimated using the method of Kaplan and Meier. Patients lost to follow up or followed until the end of the study will be censored at the time and conditions of their last visit. Standard estimates of the binomial proportion will be used to estimate and place confidence bounds on the several response rates.

12.3 Sample Size/Accrual Rate

The planned sample size is 30 patients. We estimate the accrual will be complete in 2 years, with 1-2 patients per month across the multiple sites.

12.4 Analysis of Secondary Endpoints

Overall survival, RR and toxicity data will be collected and summarized in a descriptive fashion. The analysis of the imaging correlative studies to be performed at FCCC are outlined in section 8.3.3 of the protocol.

12.5 Reporting and Exclusions

12.4.1 Evaluation of toxicity**:** All patients will be evaluable for toxicity from the time of their first treatment with pazopanib.

12.4.2 Evaluation of response: All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned

one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

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

13.1 Data and Safety Monitoring Plan

13.2 Monitoring plan

The QA Specialist / Study Monitor will monitor the medical and study records of each participant accrued at each site throughout the course of the study. In addition, the QA Specialist / Study Monitor will collect and report data to the study Principal Investigator who will review these data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the ERP and study PI as applicable.

13.3 Extramural Data Safety Monitoring Committee

Interim analysis of toxicity, outcome and ongoing scientific investigations may be performed every 6 months by the Extramural Data Safety Monitoring Committee (EDSMC). In this capacity the EDSMC will serve as an advisory committee to The ERP. The EDSMC will review those aspects of this trial that are outlined in the responsibilities section of the Extramural Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Study PI, the Extramural Research Committee and Division Medical Director, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Study Principal Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

14.1 Administrative

This study will be conducted in accordance will local, state and Federal regulations and according to accepted good clinical practice guidelines.

14.2 Data Reporting

The QA Specialist / Study Monitor will request case report form submission upon resolution of outstanding queries. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit. Participating sites are

responsible for submitting case report forms to the the QA Specialist / Study Monitor within two weeks of request.

The QA Coordinator is responsible for compiling and submitting data to the study PI and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Extramural Data and Safety Monitoring Committee.

The ERP Regulatory Coordinator is responsible for distributing and tracking review of all IND Action Letters, Safety Reports, study specific Serious Adverse Events

14.3 Retention of Records

Time points for the retention of records are described in detail in the contract between the grantor and ERP and passed on to the participating site. Please refer to the study specific terms for specific time points. In all cases the QA Specialist / Study Monitor must be notified of any plans to move records to an offsite location prior to doing so. The QA Specialist / Study Monitor will notify the ERP Regulatory Coordinator.

14.4 Study Agents

Any study agent supplied through the ERP from the manufacturer or a third party distributor may not be used for any purpose outside the scope of this protocol. The agent may not be transferred to any party not participating in the clinical trial.

15.0 References

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Appendices:

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

Determination of Creatinine Clearance (Cl_{CR})

Estimation of creatinine clearance using Cockroft and Gault method:

Cl_{CR} for males (mL/min) = $\frac{[140 - \text{age (years)}] \times [\text{weight (kg)}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$

Cl_{CR} for females (mL/min) = $\frac{(0.85) \times [140 - \text{age (years)}] \times [\text{weight (kg)}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$

For SI units:

Cl_{CR} for males (mL/min) = $\frac{[140 - \text{age (years)}] \times [\text{weight(kg)}] \times (1.23)}{[\text{Serum creatinine (}\mu\text{mol/L)}]}$

Cl_{CR} for females (mL/min) = $\frac{[140 - \text{age(years)}] \times [\text{weight(kg)}] \times (1.05)}{[\text{Serum creatinine (}\mu\text{mol/L)}]}$

Calculation of creatinine clearance based on 24-hour urinary creatinine excretion and concurrent serum creatinine levels:

$$Cl_{CR} = \frac{C_U \cdot V}{C_{CR}}$$

Here, C_U is the concentration of creatinine in the urine (mg/dL or μmol/L, for SI units), V is the urine volume (in mL per minute of urine produced during the collection period), C_{CR} is the serum creatinine concentration (mg/dL or μmol/L, for SI units), and Cl_{CR} is the creatinine clearance in mL per minute.

APPENDIX C

Urine Protein Creatinine Ratio (UPC)

Clinical meaning of UPC

There is a good correlation between the ratio of protein concentration to creatinine concentration in a random urine sample and the amount of protein excreted over 24 hours. Creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate.

Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day.

Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day.

Normal protein excretion is <100 mg to 150 mg/24 hours and is similar for men and women.

Calculating UPC

UPC ratio = Urine protein (mg/dL) / Urine creatinine (mg/dL).

UPC ratio ≈ equivalent to grams of protein excreted in urine over 24 hrs.

Example: Subject has a urine protein = 90 mg/dL and urine creatinine = 30 mg/dL.

UPC ratio= (90 mg/dL) / (30 mg/dL) = 3

The calculated UPC ratio is 3, which correlates to roughly 3 g protein excretion in a 24-hour period.

Units for UPC ratio

Note: To calculate UPC, protein and creatinine concentrations must be expressed in the same units (mg/dL, g/L, or µmol/L). If, for example, protein concentration is expressed in mg/dL and creatinine concentration is expressed in µmol/L, conversion of one of the concentration values is required. Conversion factors are:

From	To	Conversion Factor
Conventional Units: mg/dL	SI Units: µmol/L	Multiply by 88.4
SI Units: µmol/L	Conventional Units: mg/dL	Divide 88.4

References:

Xin G, Wang M, Jian L, Xu F, Wang H. Protein-to-creatinine ratio in spot urine samples as a predictor of quantitation of proteinuria 2004. Clinica Chimica Acta 350:35-39.
NKF: NKF KDOQI Guidelines [Internet]. National Kidney Foundation; and. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Available from http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g5.htm

APPENDIX D

New York Heart Association (NYHA) Classification of Congestive Heart Failure

Class I	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities
Class II	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

APPENDIX E

Bazett's Formula

Corrected QT (QT_C) = Bazett's Formula = QT Interval / √ (RR interval)

$$QTc\ (Bazett) = \frac{QT}{\sqrt{RR}}$$

RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, *measured in seconds* often derived from heart rate (HR)
RR Interval = 60/HR

Here QT is measured in milliseconds

APPENDIX F:
Supportive Care Guidelines for Diarrhea, Nausea, and Vomiting

These general guidelines are provided to facilitate subject care in the event of diarrhea, thereby avoiding serious complications. Guidelines such as these should never replace sound clinical judgment. Experience thus far suggests that use of monotherapy pazopanib is associated with an increased incidence of diarrhea, primarily of Grade 1 or 2. In rare cases, diarrhea can be debilitating and potentially life threatening, with dehydration, renal insufficiency, and electrolyte imbalances.

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology panel for treating chemotherapy-induced diarrhea [Benson, 2004].

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel patterns should be established so that changes in patterns while on treatment can be identified. An assessment of frequency, consistency, and duration of diarrhea, as well as knowledge of other symptoms such as fever, cramping, abdominal pain, nausea, vomiting, dizziness and thirst should be taken at baseline, permitting identification of patients at high risk of diarrhea. Patients will be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the study site physician.

The NCI CTCAE Version 4.0 criteria for defining diarrhea are provided below.

Toxicity Grade	**Diarrhea (includes diarrhea of small bowel or colonic origin and/or ostomy diarrhea)**
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline
3	Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living
4	Life threatening consequences, urgent intervention indicated
5	Death

Uncomplicated diarrhea is considered mild to moderate and is defined as CTCAE Grade 1 to 2 with no complicating signs or symptoms.
Complicated diarrhea is severe and defined as CTCAE Grade 3 or 4 or Grade 1 or 2 with one or more of the following signs or symptoms: severe cramping, ≥Grade 2 nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, obvious bleeding, dehydration.

Management Guidelines

Uncomplicated diarrhea of CTCAE Grade 1 or 2:

- Hydration: have subject drink 8 to 10 large glasses (approximately 2 liters) of clear non-caffeinated liquids a day (e.g., broth or electrolyte-containing sports drinks).
- If Grade 2 diarrhea, consider dose reduction of investigational products.
- Dietary modifications: have subject stop all lactose-containing products and eat frequent, small meals
- Pharmacologic intervention using loperamide:
    - Begin loperamide at initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.
    - Continuation of loperamide is suggested until diarrhea-free for 12 hours.
    - If mild to moderate diarrhea persists for more than 24 hours, administer loperamide 2 mg every 2 hours and pursue evaluation for other treatable causes.
    - If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, discontinue study drug(s) and consider initiation of second-line agents (lomotil, octreotide).

Complicated diarrhea of CTCAE Grade 3 or 4 diarrhea or Grade 1 or 2 with complicating features requires aggressive management:

- Subject must call study site physician immediately in response to any event of severe diarrhea with or without complications as listed above.
- Hospitalization may be required for subjects most at risk for life-threatening complications.
- Interrupt investigational products until symptoms resolve; consider reintroducing at a reduced dose (discuss with Novartis Medical Monitor or designee).
- If loperamide has not been initiated, begin loperamide usage immediately at an initial dose of 4 mg followed by 2 mg every 2 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.
- If no improvement in severity after 24-hours of maximal loperamide dosing, subject must visit study site and be evaluated:
- For dehydration, use intravenous fluids as appropriate.
- Antibiotic therapy should be considered in patients, who present with signs and symptoms of bacterial diarrhea such as fever, bloody diarrhea, and presence of fecal leukocytes. Investigators should have a low threshold to start such treatment in patients with Grade 3 or Grade 4 neutropenia.

- Before initiation of antimicrobial therapy, stool cultures should be obtained. When bacterial etiology for diarrhea is suspected, study-treatment and anti-motility agents (loperamide or others) should be held.
- Intervention will be continued until diarrhea free for 24 hours.

Alternative Pharmacologic Intervention for Uncomplicated and Complicated Diarrhea

- Lomotil (dephenoxylate 2.5 mg + atropine 0.025 mg) can be used. The recommended dose is 2 tablets 4 times daily. When diarrhea is under control, a dose reduction will be attempted.
- The synthetic octapeptide, octreotide, has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses ranging from 100 μg twice daily to 500 μg 3 times daily, with a maximum-tolerated dose of 2000 μg 3 times daily in a 5-day regimen.

Nausea and Vomiting

Every attempt will be made to control nausea and vomiting in subjects who have emesis and are unable to retain pazopanib.
Routine pre-medication for nausea is not necessary, but symptomatic subjects should be treated with standard anti-nausea/anti-emetic therapy as necessary.
If a subject vomits after taking study medication, the subject will be instructed not to take a replacement dose on that same day. The subject will resume taking pazopanib at the next scheduled dose on the following day. If vomiting persists, then the subject should contact their physician.

To prevent or treat nausea and vomiting standard medications are recommended. Depending upon approved medications in your region, these may include: 5-HT_3 receptor antagonist (granisetron, ondansetron, dolasetron mesylate); NK-1 receptor antagonists such as aprepitant, metoclopramide, phenothiazines (prochlorperazine); corticosteroids, (dexamethasones, prednisone); and cannibinoids (dronabinol).

WARNING: Ondansetron Safety.

Ondansetron (Zofran) IV: Drug Safety Communication - QT prolongation

AUDIENCE: Oncology, Surgery, Gastroenterology

ISSUE: The U.S. Food and Drug Administration (FDA) is informing healthcare professionals and the public that preliminary results from a recently completed clinical study suggest that a 32 mg single intravenous dose of ondansetron (Zofran, ondansetron hydrochloride, and generics) may affect the electrical activity of the heart (QT interval

prolongation), which could pre-dispose patients to develop an abnormal and potentially fatal heart rhythm known as Torsades de Pointes.

There were changes to the Zofran drug label to remove the 32 mg single intravenous dose. The updated label will state that ondansetron can continue to be used in adults and children with chemotherapy-induced nausea and vomiting at the lower intravenous dose recommended in the drug label, a dose of 0.15 mg/kg administered every 4 hours for three doses; however, no single intravenous dose should exceed 16 mg. Information from the new clinical study will be included in the updated drug label.

BACKGROUND: Zofran (ondansetron) is in a class of medications called 5-HT3 receptor antagonists. It is used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy and surgery. FDA will evaluate the final study results when available, and will work with Novartis to explore an alternative single dose regimen that is both safe and effective for the prevention of chemotherapy-induced nausea and vomiting in adults.

RECOMMENDATION: The new information on QT prolongation does not change any of the recommended oral dosing regimens for ondansetron. It also does not change the recommended lower dose intravenous dosing of ondansetron to prevent post-operative nausea and vomiting.

- The use of a single 32 mg intravenous dose of ondansetron should be avoided. New information indicates that QT prolongation occurs in a dose-dependent manner, and specifically at a single intravenous dose of 32 mg.
- Patients who may be at particular risk for QT prolongation with ondansentron are those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or patients taking concomitant medications that prolong the QT interval
- Electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia) should be corrected prior to the infusion of ondansetron.
- The lower dose intravenous regimen of 0.15 mg/kg every 4 hours for three doses may be used in adults with chemotherapy-induced nausea and vomiting. However, no single intravenous dose of ondansetron should exceed 16 mg due to the risk of QT prolongation.
- The new information does not change any of the recommended oral dosing regimens for ondansetron, including the single oral dose of 24 mg for chemotherapy induced nausea and vomiting.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of this product to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Complete and submit the report Online: www.fda.gov/MedWatch/report.htm

- Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

Read the MedWatch safety alert, including a link to the Drug Safety Communication, at:

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm310219.htm

References:

Benson AB, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA, et al., Recommended Guidelines for the Treatment of Cancer-Inducted Diarrhea. J Clin Oncol. 2004, 22; 2918-26.

U.S. Food and Drug Adminstration (FDA), GlaxoSmithKline (GSK); (6/2012) http://www.fda.gov/Drugs/DrugSafety/ucm310190.htm

APPENDIX G

Pazopanib Pill Diary

Pazopanib Pill Diary

OER-SAR-043-_____ Initials_____ Weeks_____ Page 1

OER-SAR-043 Phase II Study Evaluating the role of Pazopanib in Angiosarcoma

Instructions: The study coordinator will write in the dose you are supposed to take in the top row. In each row write the time you took that day's dose. Pazopanib should be taken once every day without food. Pills should be taken at least 1 hour before or 2 hours after eating. Pills should be swallowed whole. They cannot be crushed or broken. You should try to take the pills at about the same time every day. If you vomit after taking the tablet(s), you must not take another dose that day. You should take your next dose 1 day later at about the same time.

When the form is complete please initial it at the bottom and return the form to your study coordinator.

Pazopanib Dose_____mg Number of pills_____for each		**Comments**
Date	**Time**	Write any reason you had to miss a dose. Write any side effects here. Write down any medications you take for side effects. And write down any thing else you think may be

Patient Initials_____ Date Reviewed by Coordinator & Initials_____